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HYPOTHYROIDISM IN CHILDHOOD

III. THE EFFECT OF WITHDRAWAL OF THYROID THERAPY UPON THE SERUM CHOLESTEROL. RELATIONSHIP OF CHOLESTEROL, BASAL METABOLIC RATE, WEIGHT AND CLINICAL SYMPTOMS[1]

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THE WRITERS have reported in a previous paper (1) that the concentration of the serum cholesterol of hypothyroid children whom they studied before treatment varied from 145 mg.% to 660 mg.%, whereas in normal children it varied from 96 to 308 mg.%. These ranges overlap. A very high cholesterol concentration is suggestive of hypothyroidism in the absence of nephrosis, diabetes or liver disease. A low serum cholesterol before treatment does not necessarily exclude hypothyroidism.

Bronstein (2) in 1933, in a study of hypothyroid children, mentioned that when thyroid treatment was discontinued, the serum cholesterol rose and that the rise was of diagnostic value. In 1934, Dr. Robert Goodkind (3), while making psychiatric studies of the results of treatment in hypothyroid children, at the Harriet Lane Home, discontinued thyroid for the purpose of establishing a diagnosis by observing a return of clinical symptoms. During periods of one to three months after omitting thyroid, he made observations on the basal metabolic rate and serum cholesterol, and found that the serum cholesterol increased to high concentrations and that the basal metabolic rate decreased at the same time.

We were familiar with Goodkind's results and our attention was attracted by the fact that, in general, the concentrations of cholesterol which he found after the withdrawal of treatment were higher than those which we usually encountered in hypothyroid children before treatment. Subsequently, we have made similar observations on 17 hypothyroid children. Some of these children came to the clinic for diagnosis after having received thyroid medication for considerable periods. Since satisfactory data concerning their condition before treatment were not available, and since they presented no signs of hypothyroidism on first coming under observation, thyroid was discontinued for diagnostic purposes. Other

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TABLE 1. SERUM CHOLESTEROL AFTER WITHDRAWAL OF THYROID TREATMENT, BY WEEKS

Series No.	Harriet Lane history No.	Age before treatment	Cholesterol before treatment	Dose of thyroid	Cholesterol during treatment	Age when treatment discontinued	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Increase	Maximum value
							Hypothyroid Children																					
		yr.	mg.%	gr.	mg.%	yr.																					mg.%	mg.%
1	80612	1	145	2	140	5½				232		308															168	308
2	A-8617			½	258	4½					462																204	462
3	A-2207			1½	272	4½				414																	142	414
4	A-6522			¾	196	8½						400															204	400
5	A-12338	3 mos.	160	½	160	5 mos.			202				244				258										98	258
6	56709			2	587	7				419																	?	419
7	A-866			½	480	7½				1044			1140														660	1140
8	41005			1	171	16	201	280	288	295	288	272	276		268			291					330			159	330
9	A-9401	1	224	2	171	22 mos.							310														139	310
10	A-3941	5½	200 272	2½	162	6½	152			262	296																144	296
11	49616			3	178	15½		163				237															59	237
12	87900	8¾	660	3	200	12½		250	330	320	430	502															302	502
13	95193	13½	265 304	2½ 3	198 223	14 15½		310		365	340	255			372 365												174 142	372 365
14	47498			3 3 3	115 219 160	14½ 15½ 16½	191	210				302 210	270		302	300 230	302	358	342			371	401 247			155 182 87	270 401 247
15	58209	17	323	5 8	161 169	18½ 19½		316		410	455	512	572 469	355			380			335					374	369	411 300	572 469
16	94436	2½	203 240	3		5½	Intermission of unknown duration																					373
17	85885		201 290	3		5½	Intermission of unknown duration																					440
							Control Cases																					
18	(R) F.D.			1	147	22	145	188	180	170	160	135	160		140												41	188
19	(P) E.W.				265					305								290									40	305
20	63926	10½	240	5	200	11½	176		204	232	240	232															40	240
21	66531			3	130	13									140												10	140
22	(R) C.B.		163	3	106	14		112		139		150			135												44	150
23	(R) J.H.		132	3	109	10		110		128		130															21	130
24	(R) W.G.		105	3	61	13		86		95		90															34	95
25	(R) C.H.		164	3	117	7		150		126		150															33	150
26	(R) H.E.		181	3	161	9		225		188	212			216		188											55	216
27	(R) M.S.		173	3	133	12		140		160		139			135												27	160
28	(R) E.H.		140	3	117	13	103		139		150			124													33	150
29	A-9897		194	1	133	12					155	182									147						49	182
30	(P) N.S.			3	117					135																	18	135

children in the series had been studied before and during treatment, and the thyroid medication was omitted merely for the purpose of this study. Except in the case of a few children who were hopelessly defective in mentality, it was not considered justified to withhold therapy for longer than two or three months. As controls, similar studies were made on 13 children who were not hypothyroid. Seven of these were mentally retarded institutional children, who were of normal height and physical development. They were given 3 grains (196 mg.) of desiccated thyroid daily for a period of 8 weeks, during which there was a definite decrease in the concentration of serum cholesterol in every case. Thyroid was then discontinued and the determinations of the serum cholesterol were made during the following 8 to 10 weeks. The other 6 children of the control group had previously been suspected of having hypothyroidism and had been treated, without any apparent change in their condition. That hypothyroidism did not exist has been confirmed by the fact that no physical signs developed after the withdrawal of therapy and no change has resulted since.

In figure 1 are shown the concentrations of serum cholesterol of hypothyroid children before treatment and during treatment, and the maximum cholesterol concentration which was observed in 16 hypothyroid children within a period of 6 weeks to 4 months after discontinuing treatment. In comparison are shown the cholesterol concentrations of normal, untreated children; of normal children receiving thyroid; and of normal children after discontinuing thyroid treatment. If 300 mg.% is regarded as approximately the upper limit of normal, it is seen that only two hypothyroid children had a concentration of serum cholesterol below this level after the withdrawal of treatment, while many hypothyroid children had lower values before treatment. Normal children, after discontinuing thyroid therapy, did not show high cholesterol concentrations. There were, however, one or two borderline values in each group.

In table 1 are recorded the cholesterol values of the

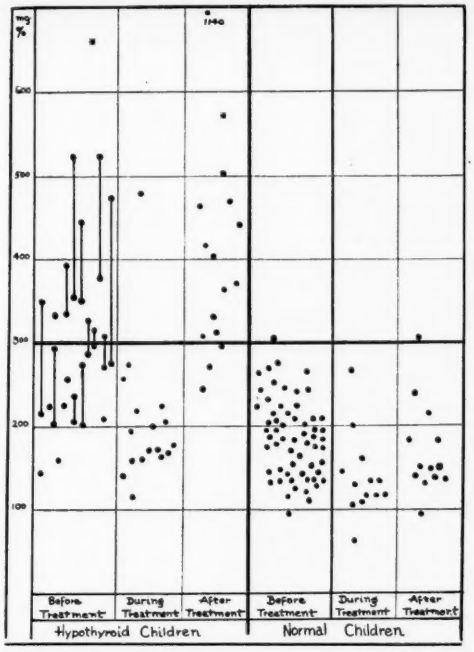

Fig. 1. Serum cholesterol, before treatment and after the withdrawal of treatment.

17 hypothyroid and 13 normal children upon whom repeated studies were made for periods of 4 to 20 weeks after discontinuing thyroid medication. In the hypothyroid group, the maximum concentrations in 14 cases were between 308 mg.% and 1140 mg.%, and, in the 3 other cases (*10*, *5* and *11*) were 296, 258 and 237 mg.%, respectively. In most cases in which the serum cholesterol had been determined before treatment, the maximum concentration observed after the withdrawal of medication was higher than the original level. The increase in the concentration of cholesterol above the level during treatment was between 98 and 411 mg.% in 15 cases. In one, *case 7*, the increase was much greater: 660 mg.%, and in one, *case 11*, there was only a small increase: 59 mg.%. In the normal patients, the serum cholesterol reached a maximum concentration of 305 mg.% in one case; in the other cases it varied from 95 to 240 mg.%. After discontinuing thyroid medication, the increase amounted to 10 to 55 mg.%.

The patient (*case 7*) whose cholesterol rose to 1140 mg.% and the cretin (*case 11*) whose cholesterol increased only 59 mg.%, reaching a maximum of 237 mg.%, are worthy of special mention. Patient 7 was a typical cretin, who had been treated intermittently and inadequately. While she was receiving a dose of ½ grain (32 mg.) of thyroid daily, her serum cholesterol was 480 mg.%. After discontinuing therapy, the serum cholesterol rose to 1140 mg.%, at the end of 7 weeks. Treatment was then resumed and the cholesterol decreased to 190 mg.%. Eighteen months later she died of uremia, with a N.P.N. of 352 mg.% and blood pressure of 156/100, and autopsy showed chronic glomerulonephritis. At the time of the studies there were no clinical symptoms of renal disease and it was not suspected, although tests of the renal function were not made. At no time was there edema or other evidence of nephrosis. It is not certain whether the chronic nephritis played a role in causing the unusually high hypercholesterolemia. The patient whose cholesterol rose only 59 mg.% in 6 weeks was a cretin of 13 years whose treatment was omitted because he was suffering from acute bronchitis with fever. In 6 weeks the cholesterol rose from 178 to 237 mg.%. Other workers have shown that acute infections cause a decrease of cholesterol which may account for our failure to find a greater rise in this case.

Hypothyroid children showed individual differences in the rapidity and regularity with which the serum cholesterol increased after the withdrawal of thyroid. Figure 2 shows the cholesterol curves of 7 hypothyroid patients who were followed for 5 to 7 weeks after treatment was discontinued. The uni-

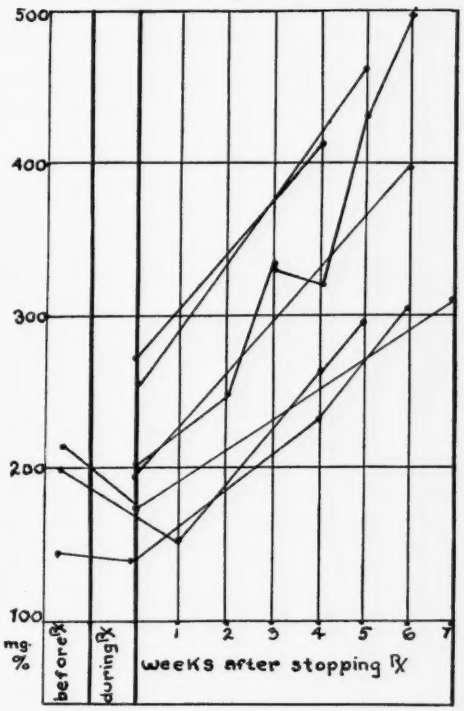

Fig. 2. Hypothyroid children. Cholesterol after discontinuing treatment.

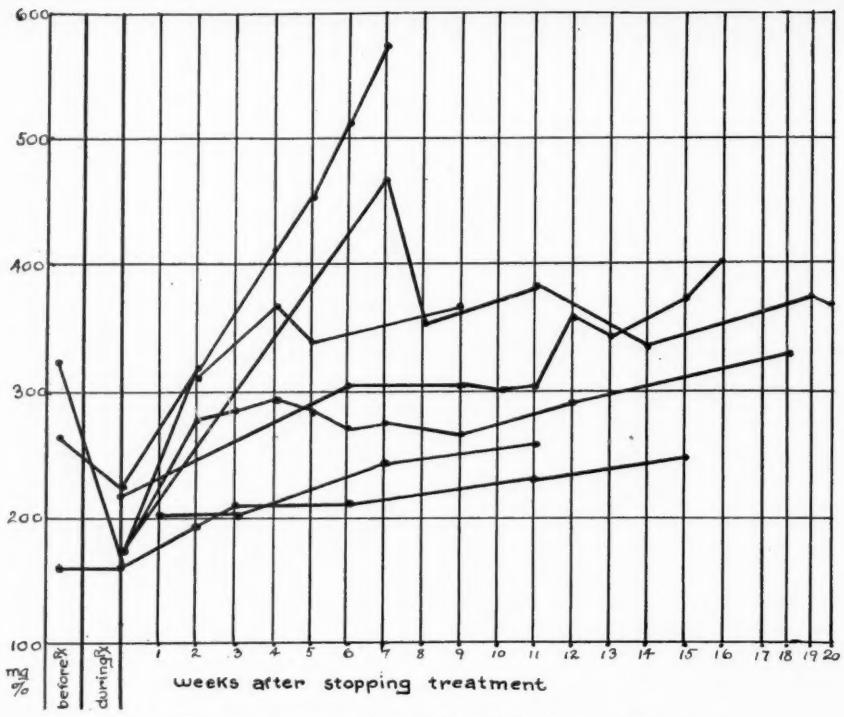

Fig. 3. Hypothyroid children. Serum cholesterol after discontinuing treatment.

formity of the rise in these cases is striking. Figure 3 shows the rise of serum cholesterol in other hypothyroid children who were followed for periods of 9 to 20 weeks. Figure 4 shows, by way of comparison, the very slight increase which occurred in the serum cholesterol of normal children who had been treated with thyroid previously.

The significance of the differences in the rise of serum cholesterol concentration, as shown in figures 2 and 3, is not certain. In some cases the cholesterol concentration rose to a peak and then dropped to a lower level. It is possible that, if determinations had been made more frequently, similar peaks would have been found in other curves. It is not known how long the high concentrations, reached in many of the cases, were maintained, because it did not seem justifiable to withhold treatment from patients for longer periods of study. Fleischmann, Shumacker and Wilkins (5) found a sharp rise in the serum cholesterol of rabbits after thyroidectomy, varying from 81 to 340% (average, 171%) above the preoperative level. After the first rise, the serum cholesterol fluctuated markedly, finally becoming stabilized after about 12 weeks at a value of 14 to 221% (average, 80%) above the base level. It is possible that if thyroid therapy had been withheld in our patients for a longer period, a decline similar to that observed in rabbits would have taken place.

The study of cholesterol after the withdrawal of treatment has been of considerable diagnostic value, especially in hypothyroid patients whose clinical signs had disappeared as the result of prolonged therapy. The rise in the serum cholesterol usually began promptly and often was sufficiently great at the end of 4 to 8 weeks to confirm the diagnosis, whereas much longer periods of observation were required before clinical evidences of hypothyroidism became unquestionable. A moderate increase in weight usually paralleled the rise in cholesterol. The first

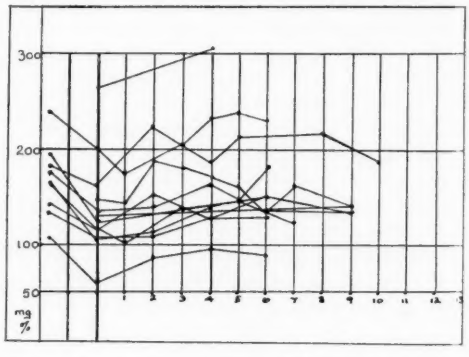

Fig. 4. Normal Children. Serum cholesterol. (First vertical division, before treatment; second vertical division, during treatment; divisions 1–13, weeks after stopping treatment.)

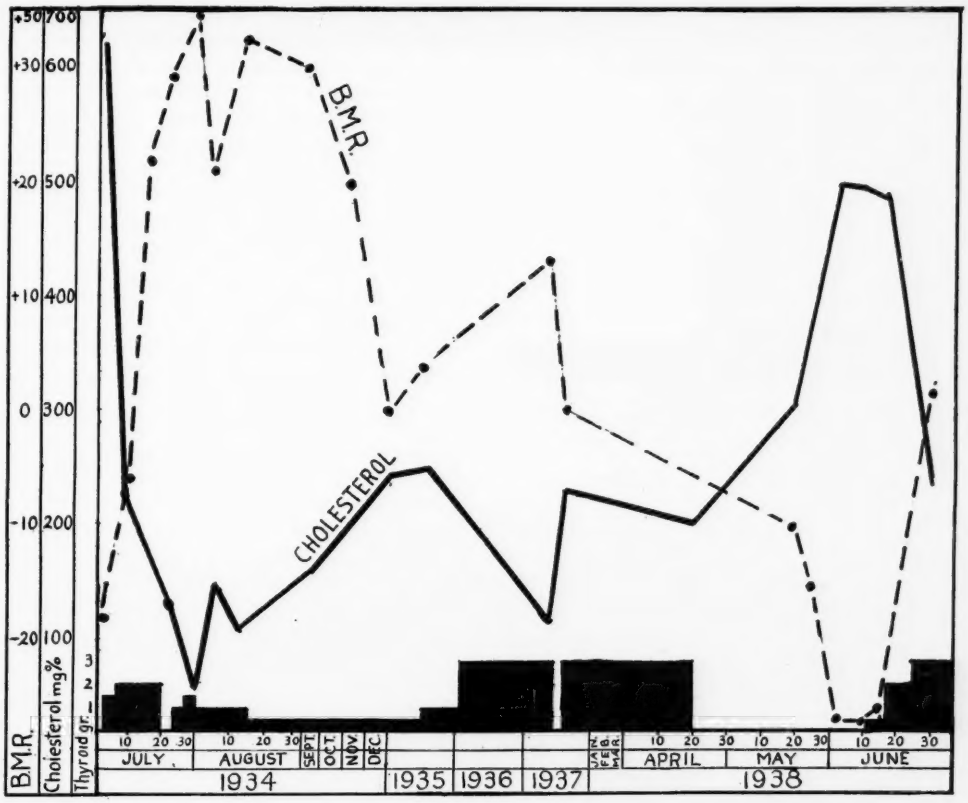

Fig. 5.

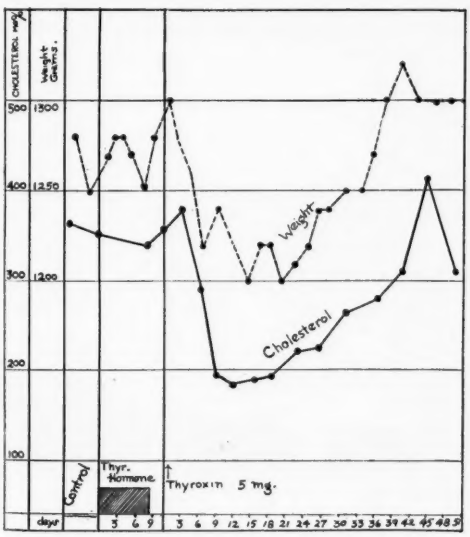

Fig. 6.

noticeable clinical change was usually a loss of color in the cheeks and lips, and a coolness and circulatory mottling of the skin, probably due to impairment of the peripheral circulation. There was moderate slowing of the pulse rate and a decrease in the pulse pressure. Otherwise, very little, if any, change was observed during the first 4 to 8 weeks. Apathy or torpor rarely appeared. The skin did not become roughened or thickened in this length of time and sweating usually persisted. There were no changes in the hair.

RELATIONSHIP OF CONCENTRATION OF SERUM CHOLESTEROL TO THE CREATINE EXCRETION, THE B.M.R., THE WEIGHT AND THE CLINICAL SYMPTOMS

In a previous study (6) of the effect of small daily doses of desiccated thyroid or of a single injection of thyroxin, it was observed that the increase in creatine excretion was the earliest and most sensitive indication of thyroid effect in children. However, the serum cholesterol of a 56-year-old myxedematous woman decreased from 715 mg.% to 515 mg.% after she had

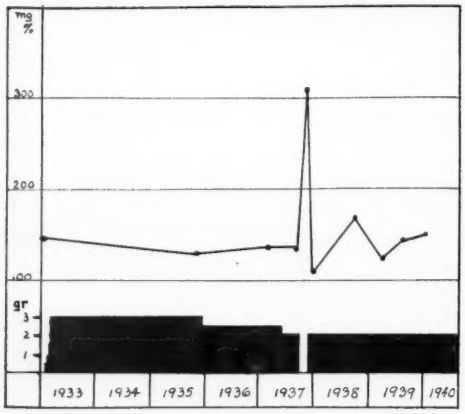

Fig. 7.

received ¼ grain (16 mg.) of thyroid daily for 2 weeks, while there was no increase during this time in the creatine excretion. In most cases, a single injection of thyroxin causes a fall in the cholesterol only a few days later than the increase in the creatine excretion. In cases in which the basal metabolic rate could be reliably measured, larger doses and a longer period of treatment with thyroid usually were required to cause an increase in the B.M.R. than to bring about a change in the creatine or the cholesterol.

In a few cases in which reliable measurements were possible there were striking reciprocal relationships between the B.M.R. and the serum cholesterol. Observations which were made on a hypothyroid child over a period of 5 years are shown in figure 5 (*case 12*). The reciprocal relationships in this case are all the more remarkable in view of the fact that the B.M.R. measurements and the chemical determinations were made by a number of different workers who knew nothing concerning the case.

In studying the effect of a single injection of thyroxin upon hypothyroid children who were receiving a constant fluid intake and a diet calculated to maintain a constant weight, a close parallelism between changes in the serum cholesterol and the changes in the body weight was frequently observed. Figure 6 shows the cholesterol and weight curves of a 2-year-old cretin who received a single dose of 5 mg. of thyroxin. It is obvious that weight changes are necessarily a less constant and reliable index of thyroid effect than the serum cholesterol because they are more influenced by diet, fluid intake and other factors.

In hypothyroid children under treatment, the level of serum cholesterol often followed the clinical response as judged by the patient's degree of activity, color and warmth of skin, pulse rate and pulse pressure. Children who were somewhat overactive and gave the impression of being slightly hyperthyroid, usually had low concentrations of serum cholesterol. Figure 7 (*case 1*) shows the cholesterol levels of a cretin who was treated continuously and intensively during a long period. The therapeutic result as judged by her rate of growth, osseous development and mental development was excellent. Throughout this period she was always slightly overactive, with a warm, moist skin, high color and fairly rapid pulse. The serum cholesterol was maintained at a fairly low level except during the period of 6 weeks when treatment was omitted. During this period, the cholesterol rose to 308 mg.%, whereas before treatment was begun it was 145 mg.%.

In some cases we have observed a gradually increasing tolerance to thyroid. Such a case is shown in figure 5. Figure 8 (*case 13*) shows the concentration of serum cholesterol in another patient who gradually became less responsive to thyroid medication. Before treatment in January, 1936, her cholesterol was 304 mg.% The dose of thyroid was rapidly increased to 2 1/2 grains (160 mg.) by February, 1936, and was continued until December, 1936. During the first 6 or 8 months, the patient was in a slightly hyperthyroid state, but the cholesterol was not determined during this period. Treatment was omitted for study from December, 1936, to February, 1937, and during this period the cholesterol rose to 372 mg.%. With the resumption of treatment, the cholesterol fell in March, 1937, to 137 mg.%. The pulse was 100 and the blood pressure was 92/48. In May the dose was increased to 3 grains (192 mg.) daily. In the course of the ensuing year, the patient became less overactive. In April, 1938, the cholesterol had risen to 223 mg.%. The pulse was 80 and the blood pressure 80/48. Another interruption of treatment during April and May, 1938, resulted in a rise of the cholesterol to 365 mg.%. Treatment was resumed in

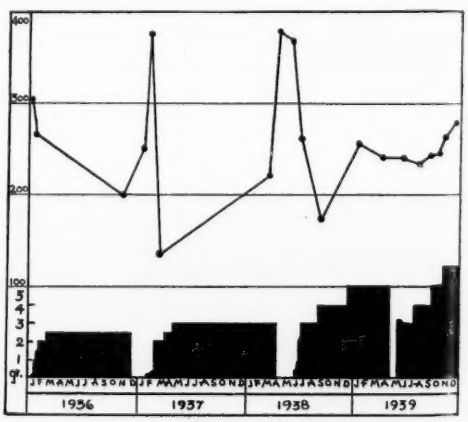

Fig. 8.

June, 1938. The cholesterol was 170 mg.% in August, 1938. Menstruation began at this time. In October, 1938, she became somewhat sluggish and the dose of thyroid was increased to 4 grains (256 mg.) daily. During 1939 the dose of thyroid was increased by steps up to 6 grains (384 mg.) daily. In spite of this, she seemed less active and alert, her color was poor and her skin was slightly cool and dry. During this period, the cholesterol varied from 240 to 279 mg.%. The B.M.R. varied from −19 to −38 (Boothby Sandiford).

In the cases just discussed there was a fairly close correlation between the level of serum cholesterol and the effects of thyroid medication as judged by clinical symptoms. Although a shift in the concentration of cholesterol may give some indication of the therapeutic effects being attained in a particular patient, no general rule can be made concerning the level of cholesterol which indicates optimal therapy. It must be remembered that there are great differences in the concentration of cholesterol of normal individuals and that the concentration may be affected by diet and factors other than thyroid activity.

SUMMARY

When thyroid medication was discontinued in hypothyroid children, the serum cholesterol increased greatly in the course of 4 to 20 weeks, reaching levels 98 to 411 mg.% above those of the treated period in 15 out of 17 cases. In a nephritic patient, the increase was 660 mg.% and in a child with an acute bronchitis it was 59 mg.%. In normal children, the withdrawal of thyroid medication caused an increase of only 10 to 55 mg.%. The concentration of serum cholesterol which was reached after the withdrawal of therapy in hypothyroid children was usually greater than that which existed before treatment was begun. The rapidity and regularity with which the cholesterol rose showed individual differences in hypothyroid children. The increase of cholesterol after the withdrawal of therapy is of considerable diagnostic value in hypothyroid children who have been treated previously because it occurs before the appearance of characteristic clinical changes.

In cases in which the B.M.R. could be measured accurately, a reciprocal relationship between the B.M.R. and the serum cholesterol was demonstrated.

In some cases a close parallelism between the cholesterol concentration and the body weight was observed.

Changes in the level of serum cholesterol often paralleled the degree of clinical response observed in hypothyroid children under treatment. Although a shift in the concentration of cholesterol may give some indication of the therapeutic effects being attained in a particular patient, no general rule can be made concerning the level of cholesterol which indicates optimal therapy, as there are individual differences in the normal level.

We wish to thank Dr. Hugh Josephs for making some of the cholesterol determinations in conjunction with studies on blood fats, carotene and vitamin A to be reported later.

We are especially appreciative of the cooperation and help of Dr. George A. Johns, Dr. George C. Medairy and Dr. Isabel McClinton in studies on patients at the Rosewood State Training School.

REFERENCES

1. Wilkins, L., W. Fleischmann and W. Block: *Journal of Clinical Endocrinology* 1: 3. 1941.
2. Bronstein, P.: *J.A.M.A.* 100: 1661. 1933.
3. Goodkind, R., and H. L. Higgins: In Press.
4. Peters, G. P., and D. D. Van Slyke: Quantitative Chemical Chemistry, Vol. I, p. 245, Williams & Wilkins Co., Baltimore, 1931.
5. Fleischmann, W., H. B. Shumacker, Jr., and L. Wilkins: *Am. J. Physiol.* 131: 317. 1940.
6. Wilkins, L., W. Fleischmann and W. Block: *Journal of Clinical Endocrinology* 1: 14. 1941.

HYPOTHYROIDISM IN CHILDHOOD

IV. THE CREATINE AND CHOLESTEROL RESPONSE TO THYROTROPIC HORMONE[1]

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IN STUDYING cases of hypothyroidism and of dwarfism, information concerning the ability of the thyroid to respond to the stimulation of the thyrotropic hormone of the pituitary should be of importance. A number of workers have tested the effect of the injection of thyrotropic hormone in adult patients by measuring the basal metabolic rate. In a few cases the effect of thyrotropic hormone upon the creatine excretion has been studied also.

Schittenhelm and Eisler (1) reported in 1932 that injection of pituitary thyrotropic hormone brought about a 20% increase in the B.M.R. of a healthy young woman, whereas it had no effect on the B.M.R. in a case of postoperative myxedema. Eitel and Loeser (2) found a rise of B.M.R. from 15 to 42% in seven days after injecting 600 U of thyrotropic hormone daily in 10 normal adults. Feuling (3) reported an increase of the B.M.R. of 15 to 19% in 57 patients in whom thyrotropic hormone was injected for 4 days. Wachstein (4) found that a patient with myxedema having a B.M.R. of −28 improved clinically after two series of 2000 and 3000 U of thyrotropic hormone given during 6 weeks. The B.M.R. rose temporarily to −2; but subsequent treatment showed that the patient had become refractory to thyrotropic hormone. The author was of the opinion that thyroid tissue was present. He noted no effect from thyrotropic treatment in a case of Simmonds' disease. Thompson (5), in 12 patients with marked myxedema, who had basal metabolic rates varying from −31 to −47, found no increase in the B.M.R. after the injection of thyrotropic hormone. In about half of 94 other patients, with thyroid disturbances varying from moderate hypothyroidism to marked hyperthyroidism, the hormone caused an increase in the B.M.R. of from 10 to 53 points; the effect was greatest in cases of mild hypothyroidism and least in patients with hyperthyroidism. Lederer (6) observed an elevation of the B.M.R. in 2 cases of pituitary insufficiency. Starr (7) found irregular responses of the B.M.R. in normal adults, but no response in 2 patients with congenital hypothyroidism and in an adult with myxedema. An adult with mild myxedema and an adolescent child with hypothyroidism responded to the same degree as normal adults. Acute temporary exacerbations were produced in 2 patients with hyperthyroidism; another was refractory to treatment and treatment was followed by a fall in metabolic rate. Scowen (8) found a rise in B.M.R. in 2 normal adults and 3 patients with pituitary insufficiency, but none in 6 adults with myxedema. In a mild case of hypothyroidism, which was supposed to be of pituitary origin, 6000 U of thyrotropic hormone caused the B.M.R. to increase from −20 to +80. Spence and Witts (9) reported a transient rise in the B.M.R. during treatment with thyrotropic hormone in 2 patients with hypopituitarism which followed the removal of pituitary tumors. In one patient the formation of antihormones was demonstrated.

Two groups of workers have studied the effect of thyrotropic hormone on the creatine excretion as well as on the B.M.R. Bulger and Barr (10) reported a rise in B.M.R. and the appearance of creatinuria in one case of pituitary cachexia, and an increase of creatinuria in a pituitary dwarf, following treatment with thyrotropic hormone. Thyrotropic hormone had little effect on the B.M.R. of a patient with a pituitary deficiency which followed removal of a pituitary tumor; creatinuria, however, was slightly increased. A patient with myxedema showed no response. Schrire and Sharpey-Schafer (11) studied the effect of thyrotropic hormone on the creatine and B.M.R. response of a large number of adults. Whereas 22 normal persons showed a response to thyrotropic hormone, 3 adults with myxedema, 1 cretin and 1 acromegalic patient failed to respond. Of 8 persons with low B.M.R., but no other signs of hypothyroidism, 5 responded and 3 failed to respond.

In a previous paper (12), the writers have pointed out the difficulties of measuring thyroid effect in children by the determination of the B.M.R. They have discussed the value of determining the blood cholesterol and the

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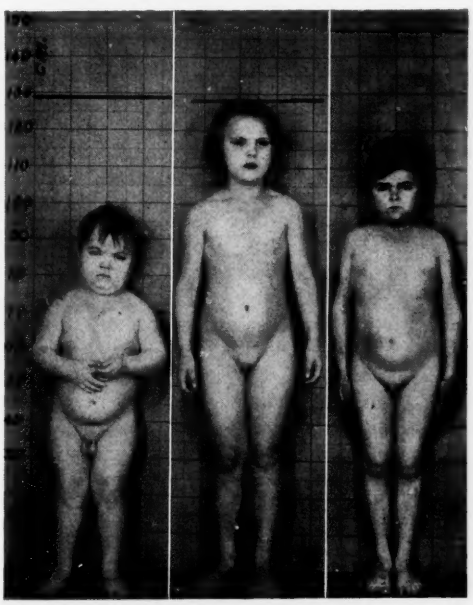
excretion of creatine in measuring the response to thyroid medication (13). It was shown that thyroid caused a marked decrease of the blood cholesterol in hypothyroid children, but very little, if any, decrease in normal children. The cholesterol response to a single dose of thyroxin presented the most striking contrast between the normal and the hypothyroid patient. On the other hand, the creatine excretion was more sensitive than the serum cholesterol as an index of the effect of thyroid administration because an increased excretion of creatine occurred not only in hypothyroid children, but also in about 80% of normal children. Thus the study of serum cholesterol after the administration of thyroid or thyroxin serves best to differentiate the hypothyroid from the normal patient, whereas the increased excretion of creatine is a more sensitive means of detecting a response to thyroid in the normal child. Pugsley, Anderson and Collip (14) have shown that thyrotropic hormone causes an increased creatine excretion in normal rats, but not in thyroidectomized rats. Pugsley (15) showed that the blood cholesterol decreases after the injection of thyrotropic hormone in normal but not in thyroidectomized rats.

In the cases to be reported, we have attempted to determine whether or not the thyroid gland was responsive to stimulation by thyrotropic hormone by observing the effect of its injection upon the creatine excretion and the serum cholesterol.



	A. Hypothyroid	B. Normal	C. Dwarf	*Group A*
Age	8–9	8–9		12–10
Height	3–9			6– 3
Bones	2–0			6– 0
Mental	3–6			10– 7
Weight	+34%			+20%
Testes	Large			Very small

METHODS

The methods of study have been described in the previous paper (12). The studies were carried out on a special metabolism ward of the Johns Hopkins hospital, or at the Children's Hospital School. Throughout the studies, the patients were given a uniform low-creatine diet, providing adequate calories and 2 gm. of protein per kg. The urinary creatine and creatinine were determined daily, the serum cholesterol was determined at irregular intervals. In each case the base level of creatine excretion and of blood cholesterol was determined during an untreated control period of 7 to 14 days. This was followed by a period of treatment with thyrotropic hormone,[2] during which daily injections were given. Following the treatment with thyrotropic hormone, no medication was given until the creatine excretion had fallen to the base level or lower. (In the discussion of data we have termed the entire period of treatment and of the subsequent return to normal as the 'thyrotropic hormone period.') Following the thyrotropic hormone period, each patient was tested either with uniform daily doses of thyroid, or with a single dose of thyroxin or with both.

The methods of investigation and the type of response to thyrotropic hormone are well illustrated by a discussion of the first 3 children whom we studied (see photograph). These were a hypothyroid dwarf of 8¾ years, his normal twin sister, and a dwarfed boy of 12¾ years who showed retarded osseous development and hypogenitalism, but presented no clinical signs of hypothyroidism. Figure 1 shows the effect of thyrotropic hormone and of thyroid upon the serum cholesterol and upon the creatine excretion, expressed in milligrams of creatine per day. The upper graph illustrates the studies made on the normal 8¾-year-old girl who weighed 80 kg. During a control period of 9 days, the average daily creatine excretion was 33 mg. and the cholesterol was 200 mg.%. Daily injections of thyrotropic hormone were now begun. The first day the dose was 50 U, or 1.8 U per kg. The second, third and fourth days 3.6 U per kg. were given daily. There was but little increase in the creatine excretion during this period. On the 5th day, the dose of thyrotropic hormone was increased to 7.2 U per kg. and this dose was continued until

[2] We have used the anterior hypophyseal thyreotropic factor of Ayerst, McKenna and Harrison, which was furnished through the courtesy of Dr. A. Stanley Cook. It is "prepared after the technic of Dr. J. B. Collip," "standardized to a potency of 50 units per cc." and "contains also small amounts of other hypophyseal factors."

the 12th day. On the 6th day, the creatine excretion began to increase markedly, reaching a peak of 294 mg. on the 8th day, after which it again decreased in spite of the continued administration of the same creatine excretion only when the thyroid gland is present. Whether the effect was due to stimulation of the secretory activity of the thyroid gland, or was due to a sudden mobilization of thyroid hormone

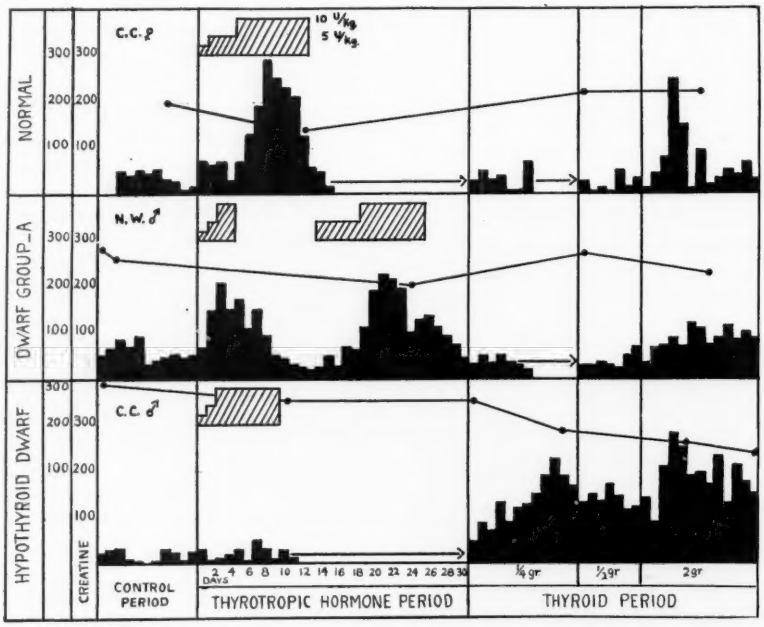


Fig. 1. THE CHOLESTEROL AND CREATINE RESPONSE TO THYROTROPIN AND TO THYROID. Bar diagram = cholesterol (first scale); curve = creatine (second scale). *c.c.* ♀ = *case 13*; *N.W.* ♂ = *case 27*; *c.c.* ♂ = *case 21*.

dose of thyrotropic hormone. After the hormone was discontinued on the 12th day, the creatine excretion fell to, or slightly below, the base level. The fourth day after the hormone was discontinued, the administration of ¼ grain (16 mg.) daily doses of desiccated thyroid was begun. During this period of 7 days, there was no increase in the creatine excretion. In a subsequent period of 7 days, during which ½ grain (32 mg.) of thyroid was given daily, the creatine excretion continued at a low level. The dose of thyroid was now increased to 2 grains (128 mg.) daily. On the third, fourth, fifth and seventh days there were greatly increased outputs of creatine but after this the creatinuria returned to approximately the base level. During the period of the administration of thyrotropic hormone, the cholesterol dropped from 200 mg.% to 120 mg.%. It rose again during the thyroid periods to 210 mg.%.

The marked increase of creatine excretion during the administration of the thyrotropic hormone was interpreted as indicating that this substance caused an increased output of thyroid secretion in the circulation, because it has been shown by Pugsley (15) that in rats thyrotropic hormone increases the stored in the gland, cannot be judged from this experiment. The fall in the serum cholesterol during the thyrotropic period was probably further evidence of thyroid effect, although caution must be used in interpreting fluctuations of cholesterol of no greater magnitude than those observed.

The absence of any creatine response to ¼ grain (16 mg.) and ½ grain (32 mg.) doses of thyroid and the very slight response to 2 grain (128 mg.) doses might be interpreted in one of two ways. It may indicate that the patient was relatively insensitive to thyroid, or that the endogenous stores of creatine had been exhausted temporarily by the thyrotropic hormone effect. We do not believe that the latter is true, because, as will be shown in subsequent cases, we have frequently observed a well marked creatine response to thyroid immediately following greatly increased excretions with thyrotropic hormone. It is of considerable interest in this case, therefore, that thyrotropic hormone apparently produced greater thyroid effect than that brought about by daily doses of 2 grains (128 mg.) of thyroid.

The middle graph on figure 1 shows the studies on a dwarf of 12 years and 10 months, who was 45.5

in. (113 cm.) tall and weighed 25 kg. His osseous development was that of a 6½-year-old boy. Although his body build was broad and stocky, he did not have the broad, infantile naso-orbital configuration or the immature skeletal proportions found in the typical hypothyroid dwarf. He was active and alert, his skin was soft, warm and his cheeks were ruddy. The penis and testes were abnormally small for his age and there were no signs of puberty. Subsequently, thyroid treatment has failed to cause an appreciable change in his condition.

During the control period, the average daily creatine excretion was 56 mg. and the serum cholesterol 260–280 mg.%. On the second day of thyrotropic injections with a dose of 4 U per kg., the creatine rose sharply. On the fourth day of treatment, the boy developed a slight cold and had a low fever. As it was feared that an infection might invalidate the interpretation of the creatine excretion, thyrotropic hormone was discontinued and the creatine excretion fell below the base level by the 9th day. As all signs of a cold had disappeared, treatment was resumed on the 13th day. Four units per kilogram were given daily for 5 days without very pronounced effect upon the creatine excretion. The dose was increased to 8 U per kg., with a marked increase of the creatine excretion during the ensuing 5 days. There was then a decrease in the creatine excretion in spite of the continuation of the thyrotropic substance. During the thyrotropic hormone period, the cholesterol dropped from 260 mg. to 204 mg. Following the thyrotropic hormone period, the patient was tested with thyroid. Daily doses of ¼ grain (16 mg.) and of ½ grain (32 mg.) caused no response and a daily dose of 2 grains (128 mg.) caused only a moderate increase in the creatine excretion, which was much less than the effect from thyrotropic hormone. The marked responses to thyrotropic hormone and the very slight response to thyroid in this patient were identical with those found in the normal girl.

In the lower graph are shown studies on a hypothyroid boy of 8¾ years, a twin of the normal girl. His height was 39 in. (99 cm.), the average for a 3½-year-old boy, and his weight was 22 kg. The patient had a bone age of 2 years and x-rays of the bones showed characteristic epiphyseal dysgenesis. The naso-orbital configuration and skeletal proportions were infantile. The cheeks and lips were pale, although the skin was not thick or rough. The genitalia were of normal size. The diagnosis of hypothyroidism has been confirmed subsequently by a marked response to thyroid treatment.

There was a low creatine excretion, averaging 18 mg. daily during the control period. The cholesterol was 290 mg.%. The dose of thyrotropic hormone was increased by the third day to 9 U per kg. and this dose was continued for 7 days. There was no effect upon the creatine excretion. The cholesterol changed only from 290 to 250 mg.%, a difference which was well within the range of spontaneous fluctuations.

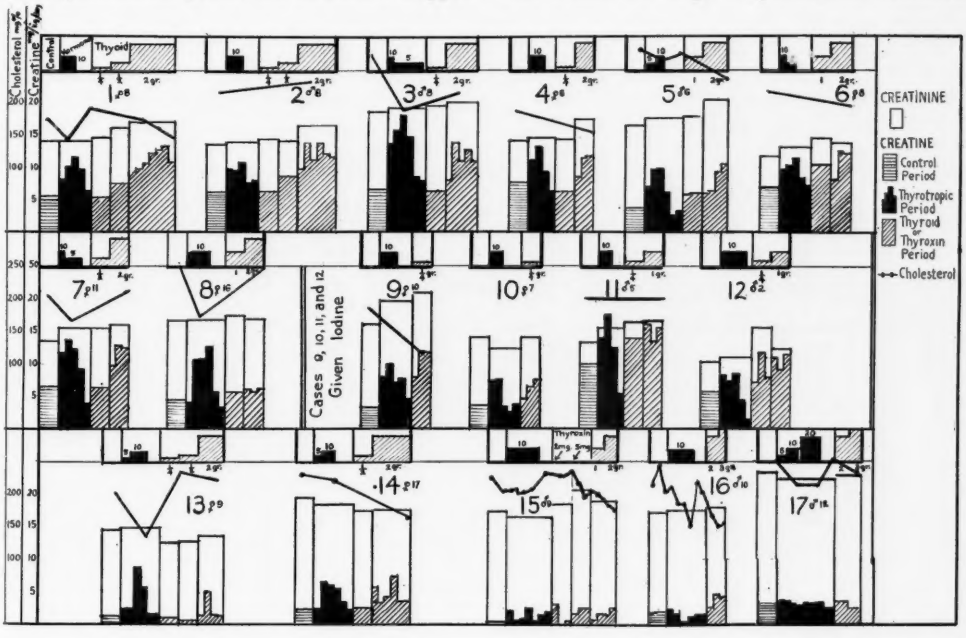


Fig. 2. The creatine and cholesterol response to thyrotropin and to thyroid in normal children.

Subsequent testing with thyroid showed a marked increase in the creatine excretion and a decrease in the cholesterol with as little as ¼ grain (16 mg.) of thyroid. This was the characteristically sensitive response to thyroid that we have previously reported in patients with hypothyroidism. The absence of any response to thyrotropic hormone, in spite of the fact that the patient was sensitive to thyroid effect, suggested that the thyroid gland was either absent or incapable of stimulation by the hormone of the pituitary.

Since the studies on the first three patients offered such striking contrasts, similar investigations were made on 3 groups of children: (*a*) 17 control children without evidence of endocrine disturbance; (*b*) 10 children with unquestionable hypothyroidism; (*c*) 9 dwarfs without clinical evidence of hypothyroidism.

NORMAL CHILDREN

The control group of 17 children consisted of 12 orthopedic patients (*cases 1–12*) without evidence of any muscular atrophy, 2 epileptic boys (*cases 15* and *16*), one normal girl (*case 13*), one undernourished girl (*case 14*) and one boy with lipodystrophy (*case 17*). The results of the studies are shown in figure 2. In this chart the creatine and creatinine outputs are expressed in milligrams per kilogram of body weight per day. The creatinine excretion for each period is shown by the unshaded blocks. The creatine output during the preliminary control period is shown by the horizontal shading. That of the thyrotropic hormone period is shown in solid black.

The excretion during the periods of treatment with desiccated thyroid or with thyroxin is indicated by the diagonal shading. During the periods of response to thyrotropic hormone and to the larger doses of thyroid, each bar represents the daily creatine averaged for a 3-day period. During the other periods in which there was little change in the creatine output, averages are shown only for the entire periods which varied from 7 to 14 days in different cases.

The creatinine excretion was not significantly affected by the administration of thyrotropic hormone or of thyroid in either the normal or the hypothyroid children, except in the case of one cretin (*case 24*, fig. 3.) This 1-year-old cretin showed mild clinical signs of hyperthyroidism following the injection of 2 mg. thyroxin and the daily average of the creatinine excretion decreased from 9 mg. per kg. to 1.7 mg. per kg.

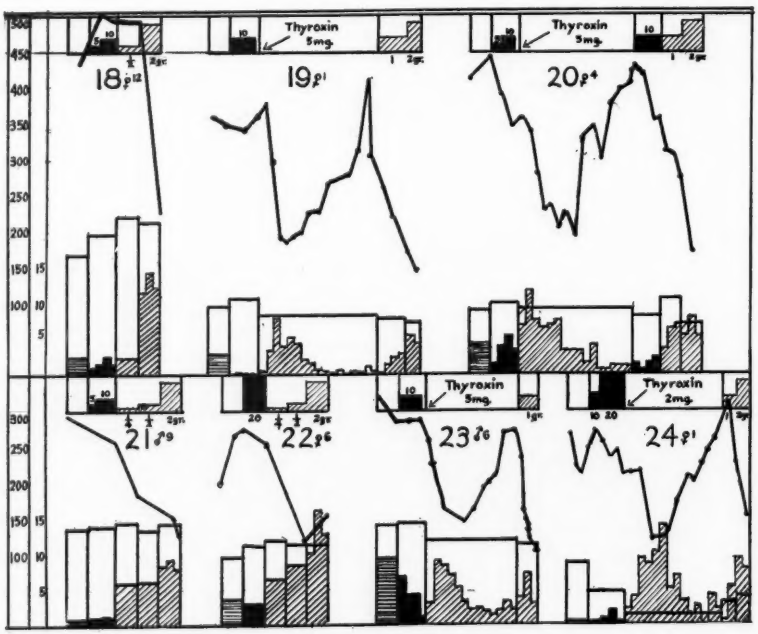


Fig. 3. The creatine and cholesterol response to thyrotropin and to thyroid in hypothyroid children.

In 14 of the 17 normal children, the creatine excretion showed a definite increase after the injection of thyrotropic hormone. In 3 cases (*15*, *16*, *17*) no response was obtained. The negative responses

will be considered later but, first, we shall consider the character of the positive responses.

The dose of thyrotropic hormone was estimated on the basis of body weight. Since the principal object was to determine whether a positive response could be obtained in all normal children, no attempt was made to determine the minimal effective dose. A dose of 10 U per kg. is comparable to the unit dose in a 100 gm. rat. In our cases, the daily doses employed were approximately 5 U, or 10 U per kg. The doses and duration of treatment are shown on the chart. In some cases, the maximal dose of 10 U per kg. was started immediately; in other instances, the first dose was 5 U per kg. and this was later increased to 10 U per kg. In several instances, (*cases* 13 and *14*), no response was obtained during a short period with 5 U per kg. but occurred when the dose was increased to 10 U per kg.

Rapidity of the creatine response. The increase in the excretion of creatine usually began very promptly, generally on the second or third day after beginning thyrotropic hormone. However, in *cases 8* and *14*, it did not begin until after the third day and, in *case 13*, not until after the sixth day. The maximum response usually occurred between the 7th and 9th days but, in several cases, it was a little earlier and, in one case, a little later.

Duration of the creatine response. In order to conserve material, the thyrotropic hormone injections were usually discontinued after the 8th or 9th day, if a marked increase in creatine excretion had occurred. After the injections were discontinued, the creatine excretion rapidly decreased to the base level or even below it. In cases in which the injections of thyrotropic hormone were continued beyond the 9th day, there was a tendency for the creatine excretion to decrease, in spite of the continued medication. This is illustrated by *cases* 3, 7, *12* and *13*. A similar observation was made on rats by Pugsley, Anderson and Collip (14), who found that creatine excretion due to the administration of thyrotropic hormone began to decline while the metabolic rate was still rising.

Whether the decrease of the creatine excretion on prolonged administration of thyrotropic hormone is due to the development of refractoriness to the hormone is not certain. A similar drop in creatine is seen also on prolonged thyroid therapy. It might be due to depletion of the stores of endogenous creatine or to increasing tolerance to thyroid.

Effect of the administration of iodine upon the thyrotropic response. In four cases (9, *10*, *11*, *12*), iodine in the form of 10 drops of Lugol's solution daily was given simultaneously with the administration of thyrotropic hormone. The chart shows that the effect of thyrotropic hormone upon the creatine excretion was in no way altered by iodine. In the literature there are differences of opinion as to whether iodine inhibits the effect of thyrotropic hormone. Siebert and Thurston (16) found that in guinea pigs the administration of iodine or iodides prevented the increase of B.M.R. which regularly followed the injection of anterior pituitary extracts. On the other hand, Friedgood (17) encountered wide variations in the effect of iodides, so that in some instances the B.M.R. response to thyrotropic hormone was not affected.

Effect of thyrotropic hormone on the serum cholesterol. In this group of cases, we were unable to make frequent determinations of the serum cholesterol. In a number of instances (*cases 1*, 3, 7, *8*, *13*, *16*, *17*), a fall in the cholesterol was observed during the administration of thyrotropic hormone followed by a rise after it was discontinued, or during the subsequent treatment with thyroid. The magnitude of the drop in cholesterol was not sufficient to justify the interpretation of this finding as a thyroid effect brought about by the action of thyrotropic hormone. Fluctuations of cholesterol as great as 80 mg. sometimes occur spontaneously (12). The writers have shown in a previous paper (13) that even large doses of thyroxin or of thyroid may cause comparatively little change in the cholesterol in normal children.

Comparison of the thyrotropic response and the thyroid response. Following the thyrotropic hormone period, the children were tested with various doses of thyroid by mouth. The creatine excretion during thyroid treatment is shown on the chart by the diagonal shading. It is seen that, in all cases except 9, *10*, *11* and *12*, the creatine excretion was very slightly increased, if at all, by daily doses of ¼ grain (16 mg.) or ½ grain (32 mg.) of thyroid. However, when 2 grains (128 mg.) of thyroid were given daily, the creatine output was markedly increased (except cases *8*, *13*, *15*, *16* and *17*). With this dose, the creatine excretion rose to levels roughly comparable to those caused by the administration of thyrotropic hormone.

Clinical response to thyrotropic hormone. There were no obvious clinical effects from the thyrotropic hormone injections. The children showed no nervousness or irritability. There was no elevation of temperature, acceleration of pulse rate or change in blood pressure.

Some children complained of pain from the injections—possibly due to the fact that the solution of hormone contained 15% alcohol. Dilution with equal parts of normal salt solution did not cause much difference. In a few cases, some redness and soreness followed the injections and occasionally there was definite induration.

Negative responses to thyrotropic hormone. Three patients out of the 17 failed to show any increase in

the creatine excretion following the injection of the thyrotropic hormone. These were:

Case 15. An epileptic boy, aged 9 years 5 months, was 52.2 in. (132 cm.) tall and weighed 23 kg. The osseous development was within the limits of normal variation. The genitalia were of normal size for age and there were no signs of adolescence.

Case 16. An epileptic boy, aged 10 years 7 months, weighed 24.5 kg. His height was 50.5 in. (128 cm.), which is the average for 9 years. The bone age was about 8 years. There were no signs suggestive of any endocrine disturbance. The genitalia showed beginning adolescent enlargement and there were a few hairs over the pubis.

Case 17. A boy, aged 11 years 10 months, whose weight was 28.3 kg., had lipodystrophy, with the characteristic absence of subcutaneous fat in the face and upper portion of the body. His height was 52.2 in. (132 cm.), which is the average height of a 9½-year-old boy. The bone age was about 9 years. The only evidence of adolescence was the presence of some fine, colorless down at the root of the penis.

These 3 patients were given large doses of thyrotropic hormone. *Case 15* received 10 U per kg. for 15 days and *case 16*, 10 U per kg. for 12 days. *Case 17* received 5 U per kg. daily for 5 days, then 10 U per kg. for 5 days and 20 U per kg. for 10 days. These doses, which were as large, or larger, than those given to any other patients, caused no increase in the creatine excretion, as shown in the chart. Subsequently, treatment with daily doses of 2 grains (128 mg.) or 3 grains (196 mg.) of thyroid caused no increase in the creatine output. *Case 15* was tested also with 2 mg. of thyroxin, and, 9 days later, with 5 mg. of thyroxin, without any effect upon the creatine. Each of these patients showed a fall of serum cholesterol during the thyrotropic hormone treatment. The decreases amounted to 55 mg., 105 mg. and 65 mg., respectively, and were comparable to the falls observed in other members of the group.

In these 3 cases, the absence of an increase of creatinuria after the injection of thyrotropic hormone could not be interpreted as indicating a failure of the thyroid gland to respond to stimulation, because no increase of creatinuria occurred after the administration of large doses of thyroid or of thyroxin. Two interpretations are possible: (*a*) These patients may be peculiarly insensitive to the usual doses of thyroid, or (*b*) they may not be especially insensitive to thyroid, but the creatine response may be inhibited by some other factors. The fact that the cholesterol fell, both with thyrotropic hormone and with thyroid, is suggestive of this, although we hesitate to stress the importance of cholesterol changes of this magnitude.

HYPOTHYROID GROUP

Studies were made on 9 typical hypothyroid children, in whom the diagnosis has been subsequently verified by marked therapeutic responses to desiccated thyroid. Brief clinical descriptions follow.

Case 18 (87900), *girl.* Juvenile hypothyroidism with onset at 4½ years. Thyroid treatment begun at 8¾ years, with marked acceleration of growth and development. Treatment discontinued 6 weeks prior to study. At time of study, age 12¾ years, height age 9½ years, bone age 10 years.

Case 19 (A-8696), *girl.* Cretin, untreated. Age 2¼ years. Height age 18 months. Bone age 12 months.

Case 20 (A-7353), *girl.* Cretin, untreated. Age 4½ years. Height age 18 months. Bone age 4 months.

Case 21 (A-2642), *boy.* Cretin (or early hypothyroidism). Untreated. Age 8½ years. Height age 3½ years. Bone age 2 years.

Case 22 (A-3924), *girl.* Cretin. At the age of 5¾ years, her height age was 15 months and bone age 4 to 6 months. Treated for 12 months with marked acceleration of growth and development. At 6¾ years, her height age was 2¾ years and bone age 4 years. Thyroid discontinued 4 weeks prior to the study. Cholesterol rose from 152 to 262 mg.%.

Case 23 (A-8088), *boy.* Cretin (or early hypothyroidism). Untreated. Age 6 years. Height age 22 months. Bone age 9 months.

Case 24 (A-9401), *boy.* Cretin. Untreated. Age 12 months. Height age 3 months. Bone development less than normal for birth.

Case 25 (34878), *girl.* Cretinism or early hypothyroidism. Untreated. Age 24 years. Height age 8½ years. Bone age 12–13 years. No epiphyseal fusions. Menstruated several times after she was 22 years old.

Case 26 (A-14200), *girl.* Juvenile hypothyroidism. Patient was apparently normal until she was 6 years old. At that time a lingual thyroid was removed and she rapidly developed symptoms of hypothyroidism. No treatment had been given. At time of study, age 10¾ years. Height age 7½ years. Bone age 7 years.

Figure 3 shows the studies on the first 7 of these patients (*cases 18–24*). In no case was there an appreciable increase in the creatine excretion upon the administration of thyrotropic hormone. The dose in each case was at least 10 U per kg. daily. In cases *22* and *24* the dose was increased to 20 U per kg. daily without effect. The cholesterol was not appreciably decreased in any case except *20*. In this patient, during the 2 periods of thyrotropic hormone treatment, the cholesterol fell 85 mg.%, and 75 mg.%. Fluctuations of this magnitude occur spontaneously in hypothyroidism.

It is of special importance that, in each case, the subsequent administration of desiccated thyroid or of thyroxin caused a very marked increase in the

TABLE 1

Case No.	H.L.H. No.	Sex	Age	Height age	Bone age	Body build	Sexual development	Onset of dwarfism	Classification[1]
			Yr. Mo.						
27	83008	M	12 10	6¼	6¾	Broad	Marked retardation	2 yr.	A
28	75271	M	13 6	5	8	Broad	Marked retardation	birth	A
29	66714	F	8 1	4¾	7	Slender	?	birth	B
30	A-7878	M	6 1	4	4¼	Broad	Normal?	2½ yr.	A
31	A-9785	M	4 6	1½	4	Medium	Normal?	birth	B
32	96026	F	4 3	2¾	3¾	Slender	?	birth	B
33	A-90	M	16 2	13¼	12½	Medium	Retardation; puberty beginning	8–10 yr.	A
34	A-13763	M	14	9½	9½	Slender	Marked retardation	?	A
35	39480	F	16	8½	14½	Medium	Marked retardation	?	A

[1] Dwarfs showing marked retardation of osseous development were classified as Group A, those with approximately normal development as Group B.

creatinuria and a marked fall in the serum cholesterol. This shows that the failure of thyrotropic hormone to increase the creatinuria was not due to inability of the creatine metabolism to react to thyroid effect. Unlike the 3 normal children who had no increase in creatinuria after thyrotropic hormone and who proved subsequently to be unresponsive to thyroid or thyroxin, these hypothyroid children showed the increased sensitivity to thyroid in small doses which has been described in a previous paper (13).

DWARF GROUP

Similar studies were made on 9 dwarfs who had no clinical evidences of hypothyroidism and who have subsequently failed to show an appreciable acceleration of growth under thyroid treatment. That they showed considerable variation in their physical characteristics is indicated by the data in table 1.

The effects of thyrotropic hormone and of thyroid are shown in figure 4. Five patients (*cases 27, 28, 29, 30* and *31*) had a marked increase of creatinuria after the injection of thyrotropic hormone and later an increase with thyroid therapy. The response was identical with that of most normal children (Compare *cases 1* to *14*, fig. 2). The sixth patient (*case 32*) showed a small but definite increase in the creatine excretion after receiving thyrotropic hormone and a relatively slight increase after thyroxin or desiccated thyroid. Three patients (*cases 33, 34* and *35*) showed no increase in the creatine output either with thyrotropic hormone or with thyroid or thyroxin. In this respect they resembled 3 boys of the control group (*cases 15, 16* and *17*) in having a 'false negative' response, and differed from the hypothyroid patients who failed to react to the hormone, although they were especially sensitive to thyroid. The three dwarfs having a 'false negative' creatine response were a 14-year-old boy who showed no signs of adolescence, a 16-year-old boy with only the earliest evidences of puberty, and a 16-year-old girl who showed no signs of puberty.

In all cases there were small decreases in the serum

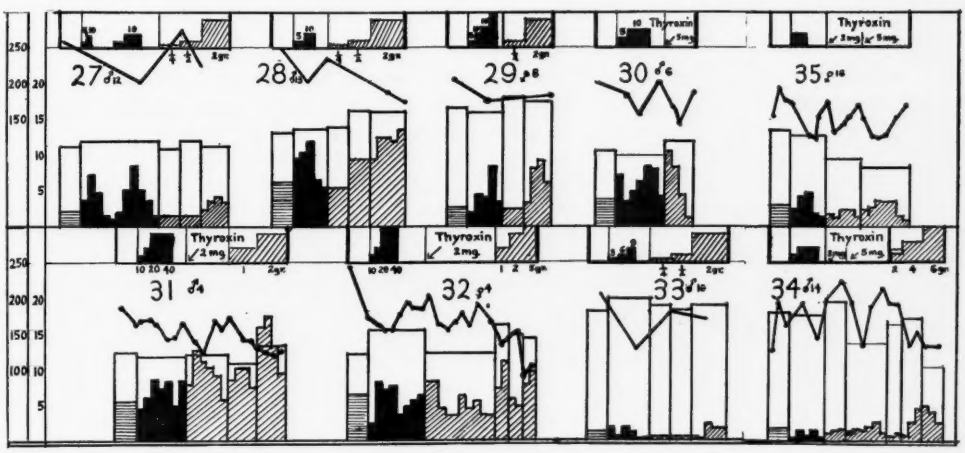


Fig. 4. THE CREATINE AND CHOLESTEROL RESPONSE TO THYROTROPIN AND TO THYROID IN DWARFS, *group A* AND *B*.

cholesterol during the administration of thyrotropic hormone and a return to the base level after it was discontinued. The decrease in the cholesterol concentration occurred in the three dwarfs who showed no creatine response, as well as in other members of the group. The decrease amounted in most cases to 50–80 mg.%, which is as great as that found in normal children after the administration of 2 grains of thyroid daily, or of a 5 mg. dose of thyroxin (13). However, since spontaneous fluctuations of this magnitude were encountered in normal children (12), it is not justifiable to interpret such a decrease as an effect of the thyrotropic hormone.

DISCUSSION

As pointed out previously, the increase of creatinuria is usually the most sensitive measurement of thyroid effect in normal as well as hypothyroid children. In studying the increase of the creatine output of children following the injection of thyrotropic hormone and then comparing the effect of the administration of thyroid, we encountered 3 types of response.

(*a*) A *positive response* consists of an increased creatinuria both with thyrotropic hormone and with thyroid medication. Since thyrotropic hormone causes increased creatinuria in normal but not in thyroidectomized rats (15), one is justified in interpreting such an effect as evidence that the patient's thyroid is present and is capable of responding to pituitary stimulation. A positive response was found in 14 out of 17 control children and in 6 of 9 dwarfs.

(*b*) A *negative response* is an absence of any increase in the creatinuria after the injection of thyrotropic hormone in a patient who shows a definite increase in creatinuria with thyroid medication. The positive response to thyroid proves that the absence of thyrotropic effect is not due to insensitivity of the creatine mechanism to thyroid medication. It seems reasonable to interpret a reaction of this type as evidence that the patient's thyroid is incapable of being stimulated by the usual effective dose of the pituitary hormone. The negative response, however, does not answer the question of whether the thyroid gland is absent, is atrophied, or is merely refractory to stimulation. A negative response was found in all 9 of the hypothyroid children studied but in no other cases.

(*c*) A '*false negative response*' is the term we have employed to describe an absence of increased creatinuria not only with thyrotropic hormone but also with the usual effective doses of thyroid or thyroxin. When thyroid medication causes no increase in the creatine output, the absence of a thyrotropic effect cannot be attributed to a failure of the thyroid gland to respond to stimulation. A 'false negative response' was found in 3 control patients and in 3 dwarfs.

The results are summarized in table 2.

TABLE 2

Type of Response	Increased Creatinuria With thy. hormone	With thyroid	Normal	Hypothyroid	Dwarfs (*A* & *B*)	Total
Positive	+	+	14	0	6	20
Negative	0	+	0	9	0	9
False-negative	0	0	3	0	3	6
			17	9	9	35

The fact that some children fail to show a creatinuric response to the usual doses of thyroid, as well as to thyrotropic hormone is of considerable interest, but the reason for this is by no means clear. It is possible that such individuals are less sensitive to thyroid than the average. Several of the patients received a dose of 2 mg. of thyroxin, followed within 10 days by a second dose of 5 mg., without any effect. Others have shown no response to 3 grains (196 mg.) of desiccated thyroid given daily. Such insensitivity is probably relative rather than absolute, since one boy (*case 34*), who failed to show any effect from an injection of 5 mg. of thyroxin or from 3 grains (196 mg.) of thyroid given daily, subsequently had a slightly increased creatinuria when given 6 grains (392 mg.) of thyroid daily. On the other hand, the absence of the usual creatinuric response may not necessarily indicate that the patient is relatively insensitive to thyroid, but may be due to some unknown inhibitory influence upon the creatine mechanism. The possible influence of the sex hormones must be considered in this connection, and has been discussed briefly in our first paper (12). Although a number of facts suggest that the male sex hormone may inhibit the excretion of creatine, the relationship is not fully understood.

The 6 cases in which we found the 'false negative' response do not shed much light upon the problem of the influence of the sex glands. There were 2 epileptic boys (*cases 15* and *16*), having no evidence of endocrine disturbance; one boy with lipodystrophy (*case 17*) and 3 dwarfs (*cases 33, 34* and *35*). Five of the patients were boys, aged 9½, 10½, 12, 14 and 16 years, respectively, and one was a girl of 16 years. The boy of 9½ years (*case 15*) showed no signs of adolescence; the boy of 10½ years (*case 16*) and the boy of 12 years (*case 17*) showed beginning adolescence, as evidenced by slight enlargement of the testes and the presence of a few fine pubic hairs. The 14-year-old boy (*case 34*) was dwarfed, having the height of a 9½-year-old boy, and he showed no signs of adolescence. Puberty was also delayed in the

16-year-old boy (*case 33*), although the beginning of adolescence was shown by some growth of the testes and penis, and the presence of a few fine hairs. The girl of 16 years (*case 35*) had no development of the breasts or nipples. A few scattered dark hairs over the labia were the only signs of puberty. Unfortunately, we have been unable to make similar studies on other boys over the age of 9 years. Boys under the age of 9 years whom we have studied have not shown an absence of the creatinuric response to the 2-grain (128 mg.) doses of thyroid, or to 5 mg. of thyroxin. The only girl who seemed insensitive to thyroid, as judged by the absence of effect upon the creatine output, was the 16-year-old dwarf (*case 35*). A number of adolescent girls (*cases 7, 9, 14*) and one sexually mature 16-year-old girl (*case 8*), showed responses to both thyrotropic hormone and to thyroid identical with those of younger children.

A decrease in the concentration of serum cholesterol occurred with thyrotropic hormone and with thyroid medication in the patients who had 'false negative' creatinuric responses, as well as those who had positive responses. This suggests that children with the 'false negative' responses were not actually insensitive to thyroid but had some peculiarity of the creatine metabolism. However, the decreases were usually only 40 to 80 mg.%, which is within the range of spontaneous fluctuations in normal children. Of the 9 hypothyroid children, only one (*case 20*) showed any decrease in the serum cholesterol following the injection of thyrotropic hormone. In this case, the decrease was only 85 mg.%, which is not greater than the fluctuations which frequently occur spontaneously in hypothyroid patients.

Other workers have reported that some individuals who are not hypothyroid fail to show any response to the injection of thyrotropic hormone when the response is measured by the effect upon the B.M.R. Thompson (5) found about half of 94 patients who were not myxedematous showed no increase in the B.M.R. after the injection of thyrotropic hormone. In some cases, the level of metabolism before treatment was normal, in some subnormal, and in some high. The magnitude of the response was greatest in patients having low levels of metabolism. However, Thompson did not test the effect of thyroid medication upon the patients who failed to respond to thyrotropic hormone. It is possible that the absence of response was due to a relative insensitivity to thyroid, rather than the inability of the thyroid gland to react to pituitary stimulation.

The present studies were undertaken in the expectation that we might find some hypothyroid children who respond to thyrotropic hormone and others who are incapable of responding. The presence of a positive thyrotropic response in a hypothyroid individual would indicate that the patient's thyroid gland is present and capable of stimulation. It would suggest the possibility that the thyroid deficiency might be secondary to a pituitary deficiency. Of the 9 typical hypothyroid patients reported here, none has shown any response to thyrotropic hormone. Subsequently, we have studied a 19-year-old girl who is dwarfed, sexually immature and presents conclusive evidences of hypothyroidism but apparently shows a response to thyrotropic hormone. Her case is still being studied and will be reported in detail later.

The studies have not cast much light on the diagnosis of dwarfism which is not of the hypothyroid type. The responses to thyrotropic hormone did not differ from those of normal children. There were 6 positive responses and 3 false negatives. There were 6 dwarfs classified as *Group A* because they showed marked retardation of osseous development, and 3 as *Group B* with approximately normal development. There were likewise differences in body build, features and sexual development. The studies of the thyrotropic response showed a sharp difference between the dwarfs of these groups and the typical hypothyroid dwarfs. However, no differences were noted between dwarfs with and without osseous retardation and no correlation was found between the type of response and the physical characteristics of the members of these groups.

SUMMARY

The effect of the injection of thyrotropic hormone on the serum cholesterol and the excretion of urine was studied. As shown previously, the increase of creatinuria is the most sensitive indicator of thyroid response in children. The response to thyrotropic hormone was described and discussed in detail. It was found to be important to study the response not only to thyrotropic hormone but also to standard doses of thyroid. Three types of response are described: a 'positive' response in which there was an increased creatinuria with thyrotropic hormone and also with thyroid; a 'negative' response in which there was no effect from thyrotropic hormone but a marked increase in creatine excretion with thyroid; a 'false negative' response in which no increase in creatinuria occurred either with thyrotropic hormone or with thyroid.

Nine hypothyroid children showed negative responses. Of 17 normal children, 14 gave positive responses and 3 false negatives. Of 9 dwarfs who presented no evidences of hypothyroidism, 6 gave positive responses and 3 false negatives. The possible causes of the 'false negative' responses are discussed.

We wish to thank Dr. Walter Block and Dr. Eva Landsberg for their assistance in the creatine studies, and Dr. Hugh Josephs

for making cholesterol determinations in conjunction with studies on blood fats, carotene and Vitamin A to be reported later. Diets were planned and supervised by Colleen Cox Hambleton of the dietary department of the Johns Hopkins Hospital.

We wish to express our appreciation to Miss Irene Tabb and the directors of the Children's Hospital School for permission to carry out extensive studies on non-endocrine patients at that institution. Valuable assistance was rendered by Dr. Richard Ferguson and Miss Jean Richardson.

REFERENCES

1. Schittenhelm, A., and B. Eisler: *Klin. Wchnschr.* 11: 1092, 1783. 1932.
2. Eitel, H., and A. Loeser: *Klin. Wchnschr.* 11: 1748. 1932.
3. Feuling, M.: *Deutsch. Arch. f. klin. Med.* 176: 90. 1933.
4. Wachstein, M.: *Klin. Wchnschr.* 13: 1434. 1934.
5. Thompson, W. O., P. K. Thompson, S. G. Taylor and L. F. N. Dickie: *Endocrinology* 20: 55. 1936; *Trans. Third. Int. Goiter Conference*, Washington, 1938: p. 250.
6. Lederer, J. A.: *Rev. Belge des Sciences Med.* 7: 369. 1935.
7. Starr, P.: *Proc. Soc. Exper. Biol. & Med.* 33: 462. 1935–1936.
8. Scowen, E. F.: *Lancet* 233: 799. 1937.
9. Spence, A. W., and L. S. Witts: *Quart. J. Med.* 8: 69. 1939.
10. Bulger, J. A., and D. P. Barr: *Endocrinology* 20: 137. 1936.
11. Sharpey-Schafer, E. P., and I. Schrire: *Quart. J. Med.* 8: 195. 1939.
12. Wilkins, L., W. Fleischmann and W. Block. *Journal of Clinical Endocrinology* 1: 3. 1941.
13. Wilkins, L., W. Fleischmann and W. Block. *Journal of Clinical Endocrinology* 1: 14. 1941.
14. Pugsley, L. I., E. M. Anderson and J. B. Collip: *Biochem. J.* 28: 1135. 1934.
15. Pugsley, L. I.: *Biochem. J.* 29: 513. 1935.
16. Siebert, W. J., and E. W. Thurston: *J. Pharmacol. & Exper. Therap.* 46: 293. 1932.
17. Friedgood, H. B.: *J. Pharmacol. & Exper. Therap.* 53: 46. 1935.

PITUITARY AND ADRENOCORTICAL INSUFFICIENCY

THE USE OF SODIUM CHLORIDE IN THE TREATMENT OF HYPOPITUITARISM[1]

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THE MEDICAL MANAGEMENT of patients with hypopituitarism implies the use of substitution or supportive therapy for the correction of the various endocrine deficiencies which result from limitation of anterior pituitary function. The relative impurity and low potency of available preparations have been chiefly responsible for disappointing results which have followed the use of anterior pituitary extracts in the treatment of many such patients. Correction of the secondary thyroid and gonad deficiencies by the administration of thyroid, ovarian and testicular preparations has been somewhat more successful. It is the purpose of the present communication to emphasize the usefulness of therapy directed at the secondary limitation of adrenocortical function which occurs in some patients with hypopituitarism.

Atrophy of the adrenal cortex has been regularly observed following hypophysectomy in experimental animals (1) and in patients with Simmonds' disease (2, 3, 4). Clinical and laboratory evidences of adrenocortical insufficiency have been reported in a number of patients with hypopituitarism (5, 6). In such patients symptoms of Addisonian crisis may be precipitated by restriction of sodium chloride and may be relieved by the administration of salt and adrenal cortex extracts (7). The therapeutic use of sodium chloride for the control of latent or symptomatic adrenocortical deficiency has been found of value in the pre- and postoperative treatment of patients with tumors limiting the function of the anterior hypophysis (8) and in the medical management of selected patients with hypopituitarism. The clinical histories of two such patients are summarized below.

Case 1. A.B., a 57-year-old man, was admitted to the hospital on the service of Dr. Einar Lie in January 1938 with history of 2 years duration of fatigue, weakness and weight loss. He had lost 60 lb. during the first 8 months of the illness and had developed marked anorexia, loss of hair, dryness of the skin, loss of sexual desire and increased sensitivity to cold. Between June 1937 and September 1937 he received injections of various anterior pituitary extracts; during this time his appetite improved and he gained about 45 lb. in weight. The other symptoms remained about the same. Between September 1937 and January 1938 he had been without treatment, had lost 20 lb. and complained of increased fatigue, weakness and anorexia. Physical examination showed the patient to be poorly nourished. He appeared chronically ill. His skin was dry, smooth and of fine texture. His hair was thin and sparse. Blood pressure was 85 systolic; 58 diastolic. His weight was 154 lb. X-ray of the skull showed marked enlargement of the pituitary fossa, with thinning of the floor and of the dorsum sella. The basal metabolic rate was −30%. Blood cholesterol was 250 mg.%. Fasting blood sugar was 71 mg.%; ½ hour after 50 gm. of glucose by mouth, 180 mg.%; 1 hour, 125 mg.%; 2 hours, 61 mg.%; 3 hours, 62 mg.%.

In January 1939 the patient was readmitted to the hospital. During 1938 he had been given intrasmuscular injections of an anterior pituitary extract 3 times weekly and had taken 2 grains of desiccated thyroid daily. In spite of such treatment he had lost 40 lb. in weight and had developed extreme anorexia and marked weakness and fatigue. There was absence of sexual desire and potency. He was abnormally sensitive to cold and had ceased to perspire. He had noted decrease in size of testes and penis. On examination, the patient was apathetic, depressed and irritable. He appeared emaciated and chronically ill (fig. 1). His weight was 114 lb. His skin was dry and smooth, the beard was sparse, and there was no axillary or body hair. There were a few fine long hairs on the arms. The pubic hair was scant and of feminine distribution. Blood pressure was 108 systolic, 60 diastolic in recumbency; 92 systolic, 64 diastolic standing. The testes were small,

[1] Read at the Annual Scientific Session of the Association for the Study of Internal Secretions, June 11, 1940.

measuring approximately 2×4 cm. The prostate was very small and flat. The B.M.R. was −42%. Fasting blood sugar was 62 mg.%; one-half hour after 50 gm. of glucose by mouth, 159 mg.%; 1 hour, 102 mg.%; 2 hours, 50 mg.%; 3 hours, 54 mg.%. On the third day of a chloride depletion test he became nauseated, vomited three times, and was weak, apprehensive and exhausted. These symptoms disappeared after the intravenous administration of fluid, salt, glucose and adrenal cortex extract. During the three days of chloride depletion the serum chloride decreased from 94 to 91 M. eq. per liter and large amounts of chloride were excreted in the urine (table 1). His response to the procedure was similar to that observed in patients with Addison's disease.

During the following 25 days he was given 2 cc. of adrenal cortex extract[2] and took 10 gm. of extra salt daily. He returned on February 14 and reported increased appetite, increase in strength and an improved mental outlook. The physical findings were essentially as before except that the blood pressure was 130 systolic, 84 diastolic. The B.M.R. had increased to −11% (2 determinations). The weight was 116 lb. A second chloride excretion test showed favorable modifications in the serum and urine chloride changes. This time he developed no symptoms.

The patient continued to take 1 cc. of adrenal cortex extract intramuscularly, and 10 gm. of extra salt by mouth daily. On May 25, 1939 he weighed 145 lb. having gained 31 lb. (fig. 1). He had developed a ravenous appetite, had improved markedly in strength and endurance and was enthusiastic, cheerful and encouraged in contrast to the previous apathy and depression. The systolic blood pressure had increased to between 140 and 160, the diastolic to between 80 and 88. The adrenal cortex extract was then omitted but the administration of extra salt has been continued. The improvement has been maintained up to the present time without other medication.

Comment. This patient presented the characteristic picture of hypopituitarism accompanying a chromophobe adenoma of the pituitary. Despite the administration of anterior pituitary extracts and of thyroid substance he had continued to go down hill. In this patient, symptoms similar to those present in many cases of Addison's disease dominated the picture. After the demonstration of an abnormality of sodium chloride metabolism, therapy directed at this phase of the problem was followed by striking subjective and objective improvement. It seems probable that improvement in appetite and nutrition were important factors in the clinical response.

Case 2. J.N. was 34 years of age when first admitted to the hospital in 1933. At that time he gave a history of increased sensitivity to cold, and of gradual loss of hair over a period of 10 years. For 2 years there had been pallor, dry skin, fatigue and loss of libido. At that time he showed the typical findings of myxedema, mild anemia and a basal metabolic rate of −37%. He improved with the administration of thyroid and was followed in the clinic for several months, at the end of which time he failed to return.

On January 11, 1939 he returned to the hospital because of pain in the left lower chest, cough and expectoration of about three weeks duration. Except for a brief period in 1937 he had had no thyroid medication in the past 5 years. He had continued to work as a truck driver until 3 weeks before admission, but had complained of marked sensitivity to cold, fatigue and constipation. For three or four weeks he had complained of severe cramps in the arms and legs. Physical examination showed the patient to be very slow mentally; his memory was poor. It was impossible to elicit a detailed history. The speech was slow and halting, with deep guttural voice. His face was puffy. The skin was pale, dry, rough and scaly. The hair was thin and dry but of fine, silky texture. The eyebrows and the beard were sparse. Axillary, body and pubic hair had disappeared. There was an occasional cough, productive of thin, watery, foul, blood-tinged sputum. There were dullness, diminished breath sounds and rales over the left lower chest posteriorly. The heart sounds were distant. The blood pressure was 90 systolic, 70 diastolic. The reflexes were hypoactive, with slow response. The prostate was so small that it could not be identified.

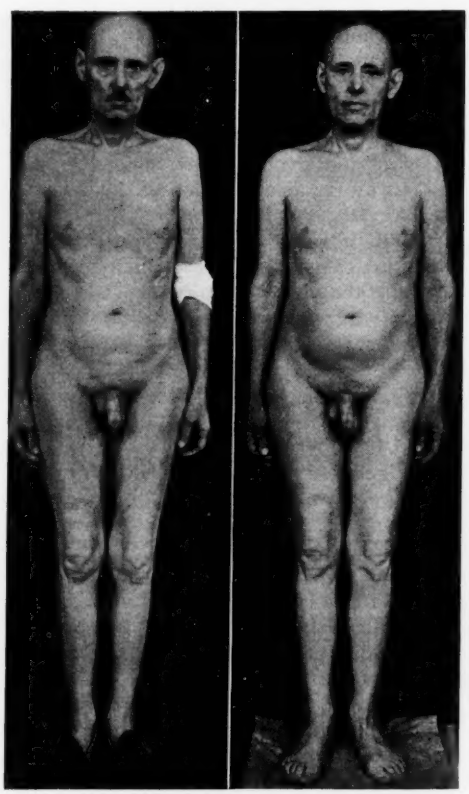

Fig. 1. PATIENT A.B., *Case 1.* Left, January 13, 1939. Right, May 25, 1939, after the administration of adrenal cortex extract and sodium chloride.

[2] The adrenal cortex extract was generously supplied by The Upjohn Company.

Blood counts were as follows: r.b.c. 2,570,000; hb. 10.4 gm.; w.b.c. 11,700. The smear and differential count were normal. The urine and stool showed no abnormalities. The blood Wassermann reaction result was negative. Blood cholesterol was 219 mg.%. Blood non-protein nitrogen was 24 mg.%. Fasting blood sugar was 74 mg.%; one-half hour after 50 gm. of glucose by mouth, 119 mg.%; 1 hour, 51 mg.%; 1½ hours, 33 mg.%; 2 hours, 45 mg.%; 3 hours 67 mg.%; 4 hours, 57 mg.%. The circulation time (arm to tongue, Decholin method) was 23 seconds. The venous pressure was 65 mm. of water. X-ray of the chest showed evidence of fluid at the left base. A small amount of fluid obtained from the left pleural cavity was slightly cloudy, contained 1,450 cells per cu. mm., of which 80% were lymphocytes. The pleural fluid was sterile and a guinea pig inoculated with the fluid showed no evidence of tuberculosis. The sputum showed no acid fast bacilli or fungi. X-ray of the gastrointestinal tract showed no abnormalities.

At the time of admission to the hospital, marked reduction in the serum chloride was observed on several occasions (fig. 2). The administration of salt for several days resulted in increase in the serum chloride level from a value of 72 to 91 M. eq. On January 21 salt was omitted and the serum chloride again fell to a level of about 80 M. eq. During this period of low serum chloride concentration, considerable amounts of salt were excreted in the urine; between January 22 and January 30 the chloride concentration (as NaCl) in the urine averaged 815 mg. per 100 cc. in spite of the low salt intake. During this period there was marked anorexia, occasional nausea and vomiting and frequent complaint of cramps in the legs. Initial determinations of the basal metabolism were −34 and −37%. On January 23, the administration of desiccated thyroid in doses of 0.130 gm. of the U.S.P. preparation daily was begun. On the evening of January 31 the patient complained of severe abdominal cramps, weakness and nausea. There was headache, profuse perspiration and vomiting. The blood pressure was 80 systolic, 60 diastolic. The administration of 1,000 cc. of 10% glucose in Ringer's solution and 200 cc. of 5% sodium chloride solution resulted in prompt disappearance of symptoms. The oral administration of sodium chloride was resumed on January 31, and the serum chloride concentration rose to a normal level within a few days. The cramp-like pains in the extremities and the anorexia, nausea and vomiting disappeared. There was gradual increase in the B.M.R., the weight decreased from 176 to 143 lb., and the puffiness of the face, mental lethargy, memory defect, and skin changes gradually decreased. There was low grade fever for several weeks, during which time the chest signs gradually cleared and eventually disappeared. Studies of the chloride excretion during sodium chloride restriction, according to the Cutler, Power and Wilder procedure (9), showed increased chloride concentration in the urine (table 1) similar to those which have been observed in Addison's disease.

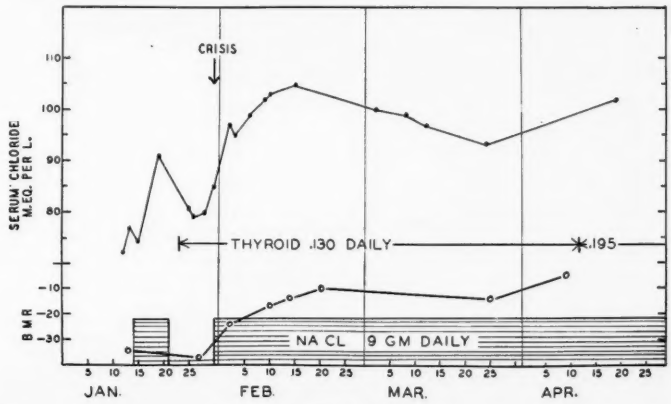

Fig. 2. Patient *J.N.*, *Case 2.*

Table 1. Chloride excretion in hypopituitarism and hypothyroidism

Patient	B.M.R.	Urine chloride (as NaCl) 4-hr. spec., 3rd day Mg./100 cc.
	Hypopituitarism	
G.T.	−47	171
J.K.	−23	65
W.S.	−26	620
J.D.	−14	494
H.B.	+ 4	364
H.S.	−22	427
T.B.	−37	503
A.B.	−42	690
J.N.	− 4	541
	Primary Hypothyroidism	
E.E.	−24	50
M.I.	−24	95
A.T.	−25	58
M.H.	−27	79
D.B.	−30	140
C.S.	−32	135
M.K.	−42	49
Controls—17 cases		111 35–244
Addison's Disease—8 cases[1]		487 382–593

[1] Includes cases of Cutler, Power and Wilder (9).

During the past year, the patient has been followed in the Out Patient Department. The evidences of myxedema have disappeared and the weight has remained constant at about 130 lb. while taking 3 grains of U.S.P. thyroid daily. The strength and weight remain sub-normal. There has been no return of hair, or of sexual desire, and there has been no increase in the size of the prostate.

Comment. In this patient, in whom an original diagnosis of myxedema was made, the administration of thyroid substance was followed by the precipitation of an Addisonian crisis, which was relieved by the administration of glucose and salt solution. Later the patient was found to respond to a standard chloride depletion test in a manner which has been found characteristic of Addison's disease (9) and some cases of hypopituitarism (7). Clinical evidences of myxedema were accompanied by prostatic atrophy, loss of sexual function, some enlargement of the sella turcica, normal blood cholesterol, and an abnormality of sodium chloride metabolism similar to that occurring in adrenocortical insufficiency. The original diagnosis of myxedema has been changed, on the basis of the above evidence, to one of hypopituitarism.

DISCUSSION

The second patient is similar in many ways to one reported by Castleman and Hertz (10) as a case of pituitary fibrosis with myxedema; their patient died with symptoms interpreted as those of adrenal insufficiency following the administration of thyroid and thyroxin. Lerman and Salter (11) also mention a patient with myxedema secondary to pituitary deficiency in whom the administration of thyroid material precipitated symptoms of adrenocortical insufficiency. Means (12) has recently described a group of similar patients as the 'pituitary type of myxedema' and has stressed the fact that in these cases thyroid therapy may precipitate an Addisonian crisis. Our experience indicates that such patients may be given thyroid safely if the adrenocortical deficiency is controlled by the administration of sufficient amounts of sodium chloride.

Theoretically, the ideal treatment of the secondary adrenocortical insufficiency in hypopituitarism would be the administration of the adrenotropic factor of the anterior hypophysis; when more refined pituitary extracts are available such replacement therapy may be feasible. In the patients whom we have studied, the use of preparations of desoxycorticosterone either by injection or by the subcutaneous implantation of pellets has been considered but has not been found necessary; the administration of adequate amounts of sodium chloride has been sufficient to prevent the occurrence of evidences of adrenal failure.

It is important to recognize latent adrenocortical insufficiency in patients with hypopituitarism, particularly in those in whom operative procedures are contemplated (8) and in those in whom the therapeutic use of thyroid substance is indicated. Castleman and Hertz (10) have stated that pituitary insufficiency should be suspected in all cases of atypical myxedema or in cases of myxedema in which evidences of other endocrine deficiencies are present. It is apparently in such patients that the administration of thyroid may be particularly dangerous. In patients of the type under discussion, a study of the clinical and electrolyte response to sodium chloride restriction has been found of value in differential diagnosis (7, 13). Table 1 summarizes the results of the application of the standardized procedure, described as a test of adrenocortical function by Cutler, Power and Wilder (9), to a group of patients with clinical hypopituitarism and a group with primary hypothyroidism. Seven of the 9 patients with hypopituitarism showed increased concentrations of chloride in the urine similar to those found in patients with Addison's disease. Four of the 7 patients developed symptoms of Addisonian crisis during the test period. Seven patients with primary hypothyroidism showed normal responses to this procedure and failed to show symptoms of adrenocortical insufficiency, either during the test period or during the subsequent therapeutic administration of thyroid substance.

SUMMARY

Evidences of latent or symptomatic adrenocortical insufficiency may occur in patients with hypopituitarism. Two such patients, in whom the administration of sodium chloride was of benefit in controlling evidences of adrenocortical failure, are described. In [illegible] patient, in whom evidences of myxedema dominated the clinical picture, the administration of thyroid substance precipitated symptoms of an Addisonian crisis. A study of the electrolyte response to sodium chloride restriction as an index of adrenocortical function is suggested as a diagnostic measure in patients with suspected hypopituitarism, particularly when an operative procedure or the administration of thyroid is contemplated.

REFERENCES

1. Smith, P. E., *Am. J. Anat.* 45: 205. 1930.
2. Silver, S.: *Arch. Int. Med.* 51: 175. 1933.
3. Galavan, M., and A. T. Stiegman: *Arch. Int. Med.* 59: 865. 1937.
4. Gunther, L., and C. B. Courville: *J. Nerv. & Ment. Dis.* 82: 40. 1935.
5. Stephens, D. J.: *Internat. Clin.* 1: 97. 1939.
6. Rose, E., and G. Weinstein: *Endocrinology* 20: 149. 1936.
7. Stephens, D. J.: *Am. J. Med. Sci.* 199: 67. 1940.
8. VanWagenen, W. P.: Neurosurgical Ward Rounds, Univ. of Rochester, 1: 6. 1940.
9. Cutler, H. H., M. H. Power, and R. M. Wilder: *J.A.M.A.* 111: 117. 1938.
10. Castleman, B., and S. Hertz: *Arch. Path.* 27: 69. 1939.
11. Lerman, J., and W. T. Salter: *Endocrinology* 25: 712. 1939.
12. Means, J. H.: *Tr. Assoc. Am. Phys.* 55: 32. 1940.
13. Stephens, D. J.: *Proc. Soc. Exper. Biol. & Med.* 43: 742. 1940.

PHAEOCHROMOCYTOMA CURED BY SURGICAL INTERVENTION. CLINICAL MANAGEMENT. ANALYSIS OF ALL REPORTED OPERATED CASES

ADRENAL MEDULLARY TUMOR

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SURGICAL INTERVENTION in cases of adrenal medullary tumor has been performed with increasing frequency in recent years. The degree of shock during and immediately following surgical removal of a phaeochromocytoma associated with paroxysmal hypertension, on analysis of the recorded cases, is unduly severe when correlated with the extent of the operation. A successful extirpation of this tumor is curative in a high percentage of the cases, as indicated in the reports concerned with the clinical, diagnostic and surgical aspects (1, 2, 3) of this disease. However, insufficient attention has been directed to those procedures, both preoperative and postoperative, which influence greatly the successful outcome of the individual case.

Those reported cases in which the tumor was attacked surgically have been selected for study to determine the factors that are important in obtaining a surgical cure. These cases are summarized in table 1, with data concerning the age, sex, clinical manifestations, diagnostic roentgenologic studies, preoperative and postoperative treatments and present condition.

We have not included in this table three cases in which death occurred during or following operations on the adrenal glands. In the first (1), preparation of the patient produced so severe a paroxysm that intervention was not attempted and the patient died two days later. Both adrenals were explored in the second (4), an enlarged adrenal was removed but the tumor-bearing gland left in situ. The patient died the next day. In the third instance (5), exploration of the right adrenal gland produced a paroxysm followed by collapse and death. The tumor was situated in the left adrenal gland. Additional fatal cases resulting from unrelated surgical or diagnostic procedures on undiagnosed patients are not listed.

General data. This selected group of 29 cases showed the greatest incidence in individuals between 25 and 45 years of age. More tumors occurred in females than in males; the tumor was more frequently found on the right side than on the left side. The tumor did not involve either adrenal in only 4 instances. Characteristic paroxysms of hypertension and associated phenomena occurred in all but 4 instances. There have been 6 deaths in this series of 29 cases. Four deaths occurred immediately after operation, one 30 days later from bronchopneumonia, and one 2 years later from metastases from the only malignant tumor in the series.

Localization of the tumor. In spite of a distinctive clinical picture that if recognized makes diagnosis relatively easy, in many cases it was somewhat difficult to determine the site of the tumor. It is important that this be done accurately for these cases do not withstand operative procedures well. In 8 cases a mass was palpated in the flank, giving presumptive localizing evidence. In some instances, though there was no palpable mass, massage over the suspected adrenal produced a typical paroxysm, thus directing attention to the proper site. It must be remembered, however, that very small tumors have occurred which were not palpable, did not displace the kidney, and in which massage did not reproduce the symptoms. These tumors have the same density as the surrounding tissues, and none has shown calcification, thus, the ordinary abdominal roentgenogram may be of little value. A very large tumor may produce sufficient displacement of other viscera to indicate its presence. The ease with which intravenous pyelography is conducted makes this a very important diagnostic procedure;

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TABLE 1

Case No. and sex	Author, reference	Age	Clinical data	Adrenal involved	Tumor size	X-rays, pyelograms	Course; postoperative medication	Follow-up
1F	Masson, Martin (6) 1923	45	Attacks of suffocation. Suspected tumor of gall bladder	R	—	—	Severe shock	Died 6 hours postoperatively
2F	Mayo (7) 1927	30	Typical paroxysms. Palpable tumor	L[1]	6×4 cm.	—	No mention of shock. Pulmonary infarct 3rd week	(L) Well to date
3F	von der Muhll (8) 1928	33	Periodic discomfort, nausea, dizziness. Mass under right costal border, slowly enlarged	R	13 cm. diam. 355 gm. (Necrotic center)	Stomach and duodenum displaced	No shock	Successful operation. Well 18 mo. later
4F	Pincoffs (9), Shipley (10) 1929	25	Typical paroxysms. No palpable mass	R	150 gm.	—	Severe shock. Transfusion, epinephrin	(L) Well to date
5M	Porter, Porter (11) 1930	39	Typical paroxysms. No palpable mass	R	Large	X-rays negative. No pyelograms	Severe shock. Transfusion	Well
6F	Lazarus, Eisenberg (12) 1932	58	No typical attacks. B.P. 156/106. Palpable mass	L	8.5×6 cm.	Flat plate positive. Retrograde: characteristic deformity	No mention of shock or medication	Successful operation
7M	Suermondt (13) 1934	23	Typical paroxysms. Palpable kidney	R	10×7×4 cm. 149 gm.	Intravenous Pyelograms: right kidney displaced	Marked shock; hypotension 2 days. Epinephrin	Well 6 mo. later. B.P. normal
8M	Bauer, Leriche (14) 1934	41	Typical paroxysms. No palpable mass	L[1]	"cherry"	Pyelograms negative	Wrong side first explored. No shock	(L): patient had typical paroxysms Feb. 1940
9M	Coller et al. (15) 1934	16	Typical paroxysms. No palpable mass	R	8 cm. diam.	Intravenous pyelograms negative	Shock. Transfusion. Saline and glucose intravenously	(L) Well 1 year later
10F	Van Goidsenhoven, Appelmans (16) 1934	35	Typical paroxysms. No palpable mass. Cholesterol 226 mg.%	L	8×6×6 cm. 135 gm.	Pneumogram pyelograms positive	Severe shock. Transfusion	Well 6 mo. later. Cholesterol 150 mg.%
11F	Kalk (17), Buchner (18) 1934	36	Typical paroxysms; reproduced by massage. No palpable mass	R	290 gm.	Intravenous and retrograde: positive	[2]Slight shock. Pneumonia	Successful operation
12F	McKenna, Hines (19) 1935	59	Precordial palpitation. B.P. variations 160–190. Palpable mass	R	12×11×9 cm.	Retrograde positive. Flat plate positive	No shock. B.P. 96/48. Malignant tumor	(L) Died 2 years later from metastases
13F	Kelly et al. (20) 1936	37	Typical paroxysms. Palpable mass	R	8.5 cm. diam. 240 gm.	K.U.B. negative. Intravenous pyelograms; ptosis right kidney, no other evidence of lesion	No shock	(L): Well, but has B.P. variations from 114/76 to 140/90. Optic fundi normal
14M	Landau et al. (21) 1936	32	Typical paroxysms. No palpable mass	R[1]	"Hen's egg"	—	No unusual shock	Died 30 days postoperatively of bronchopneumonia
15F	Burgess et al. (22) 1936	25	Typical paroxysms. Palpable mass	R	9 cm.	Downward displacement and compression of upper pole of right kidney in retrograde pyelograms	Shock—collapse. Epinephrin	Died in 3 hours pulmonary edema

TABLE I—*Continued*

Case No. and sex	Author, reference	Age	Clinical data	Adrenal involved	Tumor size	X-rays, pyelograms	Course; postoperative medication	Follow-up
16F	Beer et al. (23) 1937	26	Typical paroxysms. No palpable mass. Hypersensitive to epinephrin. Cholesterol 425 mg.%	L	9×9×6 cm. 290 gm.	Perirenal insufflation and pyelograms positive	Moderate shock. Intravenous glucose	(L) Well: April, 1940 B.P. normal
17M	Pincoffs (24) 1937	45	Typical paroxysms. Renal colic. No palpable mass	R[1]	4.5×4 ×3.5 cm. 28.5 gm.	Pyelograms negative	Immediate shock and collapse. Epinephrin with benefit	(L) Well
18F	Borch-Johnson (25) 1937	50	Atypical paroxysms. Palpable tumor in left upper quadrant	L	2000 gm.	Intravenous pyelograms: no dye left side. Retrograde: left pelvis flattened	[2]No shock. "Lacarnol"	Successful operation
19F	Borras, Mota (26) 1938	45	Typical paroxysms. Palpable tumor in right iliac fossa	R	Large	—	No shock	Successful operation
20F	Binger, Craig (27) 1938	29	No typical attacks. Variations in B.P. 120/78 to 290/120. B.M.R. +61. No palpable mass	R	6×6×3.5 cm.	Intravenous pyelograms and abdominal plate negative	First operation: left splanchnectomy. Second operation; right splanchnectomy, shock. Third operation: extirpation of tumor. Pulmonary congestion. No shock	(L) Well: June, 1940
21M	McKenzie, McEachern (3) 1938	29	Typical paroxysms. No palpable mass	R	24 gm.	Intravenous pyelograms; suspected lesion. Retrograde: produced attack	[4]Bilateral operation. Shock on removal of tumor with loss of response to epinephrin. Transfusion. Immediate improvement on adrenal cortical hormone	(L) Well: Jan. 1940 B.P. normal
22F	Brunschwig et al. (28) 1938	41	Typical paroxysms. No palpable mass	L	7×5.5×5 cm. 75 gm.	Intravenous pyelograms negative. Perirenal insufflation positive	Marked shock. Saline intravenously	(L) Well
23M	Nuzum, Dalton (29) 1938	56	Typical paroxysms. Carotid sinus pressure induced attacks. No palpable mass	R	3.5×2.5 ×2cm.	Intravenous and retrograde pyelograms negative. Perirenal insufflation positive	Shock—12 hours	(L) Well June, 1940, except for healed duodenal ulcer and silent gall stones
24F	Holst (No. 1) (30) 1938	17	Typical paroxysms. Megacolon	L	280 gm.	Retrograde: sharp bend left pelvis	Collapsed when tumor vessels clamped	Died
25M	Holst (No. 2) (30) 1938	19	Typical paroxysms. Severe retinal changes	R	"Walnut"	No pyelograms	Bilateral operation. Shock. Epinephrin	Died one-half hour postoperatively
26F	Strömbeck, Hedberg (31) 1939	39	Typical paroxysms	L	27 gm.	Intravenous pyelograms and abdominal roentgenograms negative	No shock. Incised capsule, shelled out tumor	Successful operation

TABLE 1—*Continued*

Case No. and sex	Author, reference	Age	Clinical data	Adrenal involved	Tumor size	X-rays, pyelograms	Course; postoperative medication	Follow-up
27M	Van Epps et al. (32) 1940	27	Typical paroxysms.[1] Reduced urea clearance during attacks. No palpable mass	R	4×6 cm. adherent to right adrenal	Intravenous, retrograde pyelograms, and perirenal insufflation negative	Shock. Epinephrin. Adrenal cortex extract	Pneumonia and empyema postoperatively. Well at present
28F	Eloesser (33) 1940	40	Hypertension 182/106. Large palpable mass in right upper quadrant of abdomen. No paroxysms	R	12.5×9.5×6.5 cm. Cystic	Not mentioned	Cyst broken when removed, caused sudden rise in B.P. to 190/110. No shock. Part of right adrenal removed	(L) Uneventful recovery. B.P. 130/90
29F	Authors' case. 1940	31	Typical paroxysms; induced by massage	R	11×8×6 cm. 300 gm.	Intravenous pyelograms suggestive, verified by retrograde pyelograms	[5]Shock. Epinephrin subcutaneously, intravenously, and in oil solution. Desoxycorticosterone and adrenal cortex extract. Transfusion, saline and glucose	Well 7 mo. later. Disappearance of retinal changes

The authors wish to express their appreciation and gratitude for the personal communications designated (L).

[1] Adjacent to adrenal.
[2] Preoperative medication: calcium, orally and intravenously; acid diet; parathyroid and cortical hormones.
[3] Preoperative medication: "Lacarnol."
[4] Preoperative medication: sodium nitrite; intravenous glucose.
[5] Preoperative medication: high salt diet; desoxycorticosterone acetate.

however, the results are not as satisfactory as those obtained with retrograde pyelography. Perirenal pneumograms were attempted 5 times. All the roentgenographic data of table 1 are summarized in concise form in table 2.

Preoperative and postoperative treatments. In these operated cases special preoperative medication was carried out in a limited number. In *case 11*, intravenous and oral calcium were administered in addition to an acid diet, parathyroid extract, and adrenal cortex extract. In *case 15*, sodium nitrite and intravenous dextrose were given. 'Lacarnol' (skeletal muscle extract) was given in *case 22*. One case not included in this group (1) received ephedrine preoperatively.

Shock was an important feature of 18 cases, and occurred during and immediately following surgery. There were 15 instances of severe shock, and the 4 immediately fatal cases were in this group. Of the remainder, shock was slight or moderate in 3, described as not present in 8, and not mentioned in 3. Thus shock was present in 18 cases, and not present or not mentioned in 11 cases. Postoperative shock was not present or not mentioned in the 5 cases that did not have the characteristic hypertensive paroxysms. The 4 postoperative deaths occurred in cases that had had typical paroxysms and severe postoperative shock.

The postoperative treatment recorded was in most cases the accepted routine for surgical shock, including intravenous fluids and blood transfusions. These measures proved satisfactory in most instances. In addition, epinephrin was administered and aided in maintaining the blood pressure in the period of col-

TABLE 2. X-RAY STUDIES TO DEMONSTRATE THE PRESENCE OF THE TUMOR[1]

	Abdominal plate		Intravenous pyelography			Retrograde pyelography	
	Positive	Negative	Positive	Questionable	Negative	Positive	Negative
	3	5	7	13	9	6 16	8
	6	13	11	18	17	10 18	17
	12	20	16	29	20	11 24	23
		26	21		22	12 29	27
		27			23	15	
		29			26		
					27		
Totals:	3	6	4	3	7	9	4

	Perirenal pneumograms		Not mentioned in history	No examinations
	Positive	Negative		
	10	27	1	19
	16		2	25
	22		4	
	23		5	
			28	
Totals:	4	1	5	2

[1] The numbers listed are the case numbers obtained from table 1.

lapse in 7 cases, all of which had severe shock. In the case we are presenting we also found it necessary to give epinephrin intravenously and subcutaneously in ordinary solution as well as in oil. Adrenal cortex extract was given as supplemental treatment in *cases 21* and *27*, and was recommended by Strombeck and Hedberg (31). Desoxycorticosterone acetate and adrenal cortex extract were administered in our case.

Follow-up studies. In an attempt to determine the end results of operative removal of the tumor, we communicated with authors of previous articles. Their responses are noted in table 1, and all these data are summarized briefly in table 3.

TABLE 3. FOLLOW-UP COMMUNICATIONS[1]

Reported				*Not reported*	
Alive			Dead	Probably alive	Dead
Without symptoms	With symptoms or blood pressure variations				
2	21	8	12	3	1
4	22	13	(metastases from malignant tumor)	5	14 (pneumonia)
9	23				
16	27			6	15
17	28			7	24
20	29			10	25
				11	
				18	
				19	
				26	
Totals: 12		2	1	9	5

[1] The numbers listed are the case numbers obtained from table 1.

CASE REPORT

A.B., white American saleswoman, 31 years of age, entered the Mount Zion Hospital on November 11, 1939, on the medical service of Dr. LeRoy H. Briggs, complaining of nausea and vomiting associated with headaches for the past 7 years, becoming severe 4 weeks prior to admission.

The present illness started just after her second uneventful full term pregnancy, 7 years ago, with dull aching diffuse pains in her head that lasted a few days. These headaches recurred every 3 or 4 months, and were associated with nausea and vomiting, and profuse perspiration. These symptoms would come on suddenly, and last from 5 to 15 minutes. She first consulted a physician 2 years ago, and examination revealed a slight thickening of the arteries of the optic fundi, a systolic aortic murmur, and a blood pressure that varied from 120 to 200 mm. Hg, systolic, and 75 to 120 mm. diastolic. A diagnosis of migraine headaches was made and she was given ergotamine tartrate with marked relief of her symptoms for a few months. Then the attacks recurred with increased frequency and severity and ergotamine tartrate no longer afforded relief. The patient noticed that the wearing of a tight girdle or stooping forward seemed to bring on an attack.

Two weeks prior to admission these attacks became unusually severe and on the day of admission she was seen by Dr. Clayton Mote of San Francisco. On physical examination he found her blood pressure varied from 140 to 280 mm. Hg, systolic, and 70 to 150 mm. diastolic. She had slight papilledema of the nasal one-half of each optic disc, hemorrhages and exudate in the optic fundi, and a tumor mass that was palpable in the right flank. The blood sugar concentration was 240 mg.%, the urine showed 4 + sugar. His impression was that the patient was suffering from an adrenal medullary tumor, and that these were attacks of paroxysmal hypertension.

The past medical history did not contribute anything significant with reference to the present illness.

Physical examination in the interim between attacks. The temperature was 37° C., the pulse 100, the respirations 18. The patient was a well developed, well nourished, intelligent, cooperative, white female, aged 31, who appeared to be in good health. The hair distribution on the body was normal. The optic fundi showed the left disc to have a slightly blurred edge, the right to be normal. The retinal arteries were markedly tortuous, their light streak was well marked, and where they crossed veins there was a definite compression of the veins. There were a number of small hemorrhages, mainly of the flame-shaped type, as well as numerous white patches throughout the retina. In the right eye, near the macula, there was a suggestion of a beginning star-shaped figure. The thyroid was normal in size and no nodules were palpated. The lungs were clear to auscultation and percussion. The left border of the heart was percussed 9 cm. to the left of the midsternal line, with the apex impulse in the fifth interspace. The rate was 100, the rhythm was regular. There was a blowing systolic murmur at the aortic area that was transmitted to the apex. The aortic second sound was accentuated. There was no thrill palpable. The blood pressure taken at this time was 140/100 in both arms, and 150/105 in both thighs. The peripheral arteries showed slight thickening. Examination of the abdomen revealed a tumor mass in the right kidney region which was firm, smooth, not tender; it descended with inspiration. The liver and spleen were not palpable. The neurologic, rectal and pelvic examinations revealed nothing significant.

Production of attacks. Typical attacks were produced by massaging the tumor mass in the right flank. Just prior to massage the patient was comfortable, the pulse rate was 95 to 100, and the systolic blood pressure varied between 110 and 130 and the diastolic blood pressure between 80 and 95. After a minute or so of massage the patient complained of a constricting pressure in the lower chest with a pounding headache; the respirations and pulse rate increased temporarily, and the blood pressure began to rise. At the height of the paroxysm deep sighing respirations occurred, the pulse rate dropped to between 60 and 70, the blood pressure rose to 260 to 290 mm. systolic and 150 to 180 mm. diastolic; the patient's hands and feet were cold and perspiring, and she became nauseated and vomited. Pressure over the carotid sinus did not produce or alter the attacks. These paroxysms subsided within five minutes, first the nausea, vomiting and headache suddenly stopped, then the pulse rate rose to 90 to

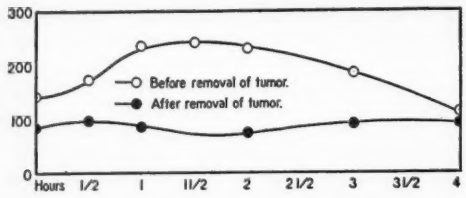

Fig. 1. DEXTROSE TOLERANCE TEST BEFORE REMOVAL OF THE TUMOR SHOWED A DIABETIC TYPE CURVE. Three weeks after removal a normal curve was evident.

100, and the blood pressure fell to 110 to 130 mm. systolic and 80 to 95 mm. diastolic. Her hands and feet became warm and the patient felt weak and "worn out."

Laboratory findings. R.B.C. was 3,100,000; Hb. 9.5 gm. per 100 cc.; W.B.C. 6150, with a normal differential count. The sedimentation rate was normal. The routine urine examination showed no abnormalities. The Mosenthal concentration test showed specific gravities varying from 1.018 to 1.028, with a night volume of 175 cc. The Wassermann and Kahn reactions were negative. The B.M.R. was −1%. The result of Friedman modification of the Aschheim-Zondek test was negative. The chloride concentration of the blood was 416 mg. per 100 cc. The spinal fluid was normal.

The results of the dextrose tolerance test performed when the blood pressure was normal are shown in figure 1.

Electrocardiographic studies on Dec. 15, 1939, when the blood pressure was normal, revealed a sino-auricular tachycardia with a rate of 115 per minute, notched P_2, diphasic P_3, slurred and slightly depressed ST 1 and 2, and marked left axis deviation. Dr. J. J. Sampson reported that this was not conclusive evidence of myocardial damage.

Roentgenologic examination by Dr. J. Levitin: "Stereoroentgenograms of the skull showed a normal sella turcica, with no abnormal skull markings. Anteroposterior and lateral plates of the chest showed the heart to be of normal size. The arch of the aorta was slightly thickened but not dilated. The lung fields were clear. An intravenous pyelogram showed a normal left renal pelvis and calices. The ureters were normal. The right kidney did not appear to function as well as the left, the right renal pelvis and calices were not well outlined."

A retrograde pyelographic study was made by Dr. H. A. R. Kreutzmann. He found that the phenolsulphonephthalein excretory function was normal, with an appearance time of 4 minutes, and a normal excretion of the dye from each kidney. Roentgenography interpreted by Dr. J. Levitin showed that the left kidney pelvis and calices were normal. The upper calices of the right kidney were displaced downward by a tumor mass of the right adrenal and there was an angulation of the upper end of the right ureter (fig. 2). The patient had no reactions from this procedure.

Psychiatric examination (by Jacob Kasanin, M.D., Dec. 16, 1939); "During the 'attacks' the patient noted a peculiar and uncomfortable sensation which seemed as though her heart was throbbing and beating rapidly. She compared this sensation with the feeling of outward excitement such as is obtained from some serious emotional situation, except that these feelings were neither related to nor provoked by an actual emotion. It was like an emotion for no reason, or an unpleasant 'thrill.' A similar feeling was noted when somebody made love to her. In these situations she would breathe deeply, her heart palpitated rapidly, and the whole feeling of excitement was all out of proportion to the degree of emotion which she was experiencing. She avoided intimate contact with men because of the embarrassment produced by these extremely emotional attacks in orderly and usual situations. These attacks had no relation to the consumption of alcohol, which, if anything, soothed rather than excited her. The psychiatric study of this patient showed a fairly stable young woman whose symptoms were the visceral somatic manifestations of emotions with the emotion as such being very trivial."

Preoperative preparation. On Dec. 16, 1939, the patient was placed on a high salt diet and an additional 4 gm. of sodium chloride daily. On Dec. 18, 1939, the day prior to surgical intervention, she received 5 mg. of desoxycorticosterone acetate[1] intramuscularly, and another 5 mg. just before the operation.

Operation (Performed by Dr. Harold Brunn and Dr. F. I. Pearl). Two hours before the operation the patient was given 0.1 gm. of seconal orally, and one hour before 15 mg. of morphine sulphate. She was placed in the supine position, and after nitrous oxide and oxygen induction, was anesthetized with semi-open ether. A Lindeman

Fig. 2. X-RAY SHOWING THE RESULTS OF THE RETROGRADE PYELOGRAPHIC STUDIES. The sharply outlined calyces of the right kidney were depressed downward, the right ureter showed a marked angulation.

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needle was tied into the antecubital vein. The patient was changed to the prone position, and the Young approach to the right adrenal was made. A tumor mass in the region of the right kidney was exposed. In attempting to free the tumor, which reached to the level of the eleventh rib, numerous vascular spaces. The stroma was scant. The cells were poorly outlined, usually polygonal in shape, and had small round nuclei containing small scattered chromatin granules and one larger chromatin mass near their center. No mitotic figures were present. Some cells had a

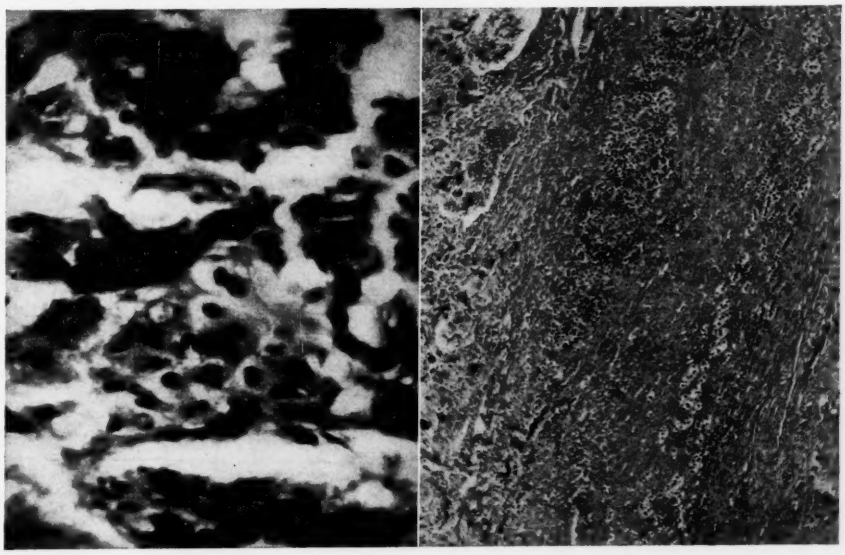

Fig. 3 (left). SECTION OF THE TUMOR SHOWING DISTINCT NESTS AND STRANDS OF CELLS WHICH VARY GREATLY IN SIZE (×300). The large dark cells are filled with fine brown granules characteristic of the chromaffin reaction. (Orth's fixation.)

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a moderately severe hemorrhage ensued. It was apparent that the tumor could not be removed through this incision. The patient was then changed into the usual kidney position and another incision was made extending from the anterior superior iliac spine to make a "T" with the original incision. The tumor was situated on the superior and lateral aspects of the kidney, the latter being compressed and deflected downward and mesad. No distinct arteries were encountered leading to the tumor; the previous hemorrhage was apparently from a vein. The intact tumor was removed after severing fibrous bands at its lower pole. It was not necessary to remove the kidney; and because of the serious condition of the patient a rapid closure was effected. The retroperitoneal space was drained.

Pathologic examination, (a) gross. The spheroid tumor was 11 ×8 ×6 cm. in size, weighed 300 gm., and was completely encapsulated by gray fibrous tissue about 1 mm. thick. On section it was composed of a reddish brown cellular tissue which had many scattered large and small hemorrhagic areas. There were several smooth-walled fluid-containing cysts varying in size up to 4 cm.

(b) Microscopic. The fibrous capsule varied considerably in thickness. The tumor had a somewhat reticulated pattern with the cells arranged in long irregular strands that seem to form the walls of the extremely large and clear, eosinophilic cytoplasm, others, after fixation with Orth's fluid or potassium bichromate, showed the cytoplasm to be filled with fine brown granules (fig. 3). These granules were especially prominent in the larger cells which often had vesicular nuclei. In a few regions adrenal cortical cells were scattered singly and in groups in fibrous tissue extensions just beneath the capsule (fig. 4). Iron stains on alcohol fixed tissue showed hemosiderin in some stromal cells adjacent to the vascular channels, but not in the tumor cells.

The pattern present in this tumor corresponded with those phaeochromocytomas previously described (34) and gave no histologic evidence of malignancy.

The samples of venous blood were analyzed[2] simultaneously, together with a normal control, and each contained approximately 0.08 micrograms of epinephrin per cubic centimeter.[3]

Analysis[2] of a representative portion of tumor, and of 10 cc. of fluid removed from a cyst in the tumor permitted

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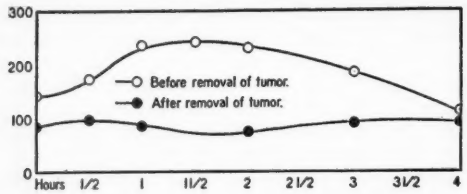

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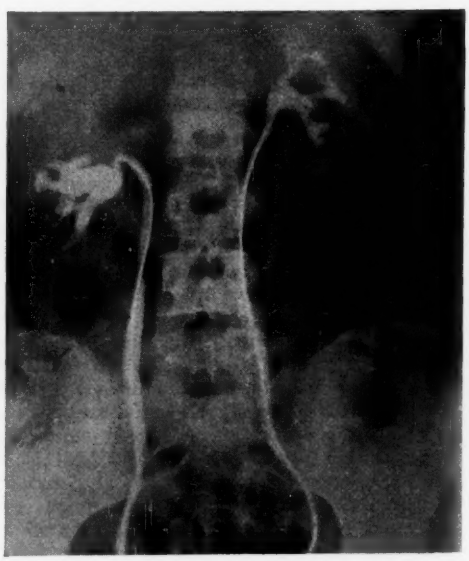

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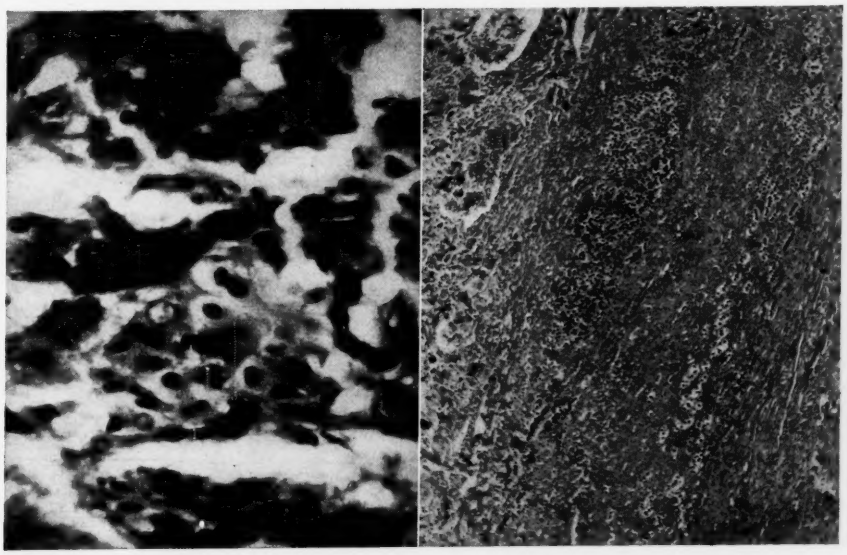

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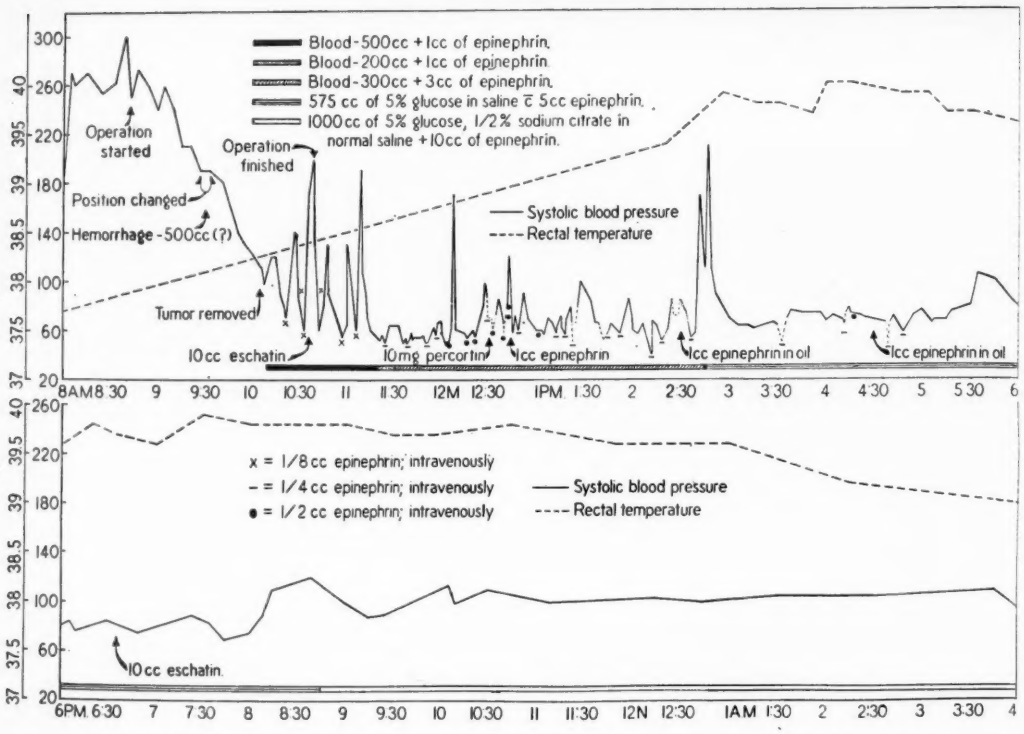
Blood-500cc + 1cc of epinephrin.
Blood-200cc + 1cc of epinephrin.
Blood-300cc + 3cc of epinephrin.
575 cc of 5% glucose in saline & 5cc epinephrin.
1000cc of 5% glucose, 1/2% sodium citrate in normal saline + 10cc of epinephrin.
Operation started
Operation finished
Position changed
Hemorrhage - 500cc (?)
Tumor removed
10cc eschatin
10mg percortin
1cc epinephrin
1cc epinephrin in oil
1cc epinephrin in oil
Systolic blood pressure
Rectal temperature
8AM 8:30 9 9:30 10 10:30 11 11:30 12M 12:30 1PM 1:30 2 2:30 3 3:30 4 4:30 5 5:30 6
x = 1/8 cc epinephrin; intravenously
– = 1/4 cc epinephrin; intravenously
• = 1/2 cc epinephrin; intravenously
Systolic blood pressure
Rectal temperature
10 cc eschatin.
6PM 6:30 7 7:30 8 8:30 9 9:30 10 10:30 11 11:30 12N 12:30 1AM 1:30 2 2:30 3 3:30 4

Fig. 5. The systolic blood pressure determinations charted were taken every 3 minutes during the first 8 postoperative hours. The blood and fluids administered intravenously, plus the additional intravenous injections of epinephrin, are indicated. The sudden drop in systolic blood pressure between the start of the operation and the time the patient's position was changed was probably due to ligating numerous vessels leading to and from the tumor.

the following conclusions: (*a*) epinephrin could not be identified as such in either specimen; (*b*) large amounts were present of a substance which interfered with the quantitative test for epinephrin in a manner characteristic of catechols, but could not be identified as such; it may be a precursor of epinephrin; (*c*) the tumor extract produced marked mydriasis of the cat's eye.

Reactions to surgery and therapeutic procedures. Figure 5 indicates the blood pressure readings, the types and amounts of fluids administered and the drugs used during the operative and immediate postoperative periods. The patient was in a paroxysm before the anesthesia was started, with a blood pressure of 186/120; the pressure rose to 300/205 when the first incision was made. The blood pressure started to drop on exposure and ligation of the tumor blood vessels. When the tumor was removed the pressure had fallen sharply to 110/92, and continued to fall to a systolic pressure of 60 in spite of supportive measures. The patient was transferred to her bed, placed in shock position, and kept in the operating room.

A continuous intravenous drip was attached to the Lindeman needle prior to surgery, but supportive therapy was not started until the pressure had fallen to 110/92. Following the operation whenever a systolic blood pressure reading of 60 mm. of mercury or less was obtained, epinephrin was injected through the tubing of the intravenous drip. Six hours after the tumor was removed, the blood chloride concentration was 300 mg.% and the rectal temperature was 39.6° C. The drop in the blood chloride concentration and the sudden temperature rise suggested the possible development of an adrenal cortical crisis; however, it was not possible to verify this with accurate electrolyte studies. The patient was then given adrenal cortex extract,[4] additional desoxycorticosterone acetate, and epinephrin in oil, all of which aided in raising and stabilizing the blood pressure. Ten hours after the tumor was removed the systolic blood pressure stabilized at 100 mm. Hg, and the rectal temperature was 39.8° C. A total of 27 mg. of epinephrin was administered in the first 12 hours after the operation. Twenty hours after the tumor was removed the blood chlorides were 525 mg.%, the rectal temperature was 38.4° C., and the blood pressure did not fluctuate significantly.

Follow-up. The wound healed by primary intention except for a small sinus tract at the site of drainage which closed completely in six weeks. The patient left the hospital three weeks after the operation, at which time her systolic and diastolic blood pressure had stabilized between 120 to 135, and 70 to 100 mm. Hg respectively. Since then she has been observed regularly at monthly

[4] Eschatin, Parke, Davis & Co.

intervals. In the past 7 months she has been in excellent health, has gained 15 lb., has had no paroxysms, and her blood pressure varies between 125 to 135 systolic, and 85 to 100 diastolic. The systolic apical and aortic murmurs have disappeared, although the second aortic sound is still slightly accentuated. A remarkable diminution of most of the flame-shaped hemorrhages and exudates in the fundi has taken place in these 7 months. The retinal arteries do not compress the veins as deeply. The paroxysms cannot be reproduced by massage of either flank. The dextrose tolerance test was repeated on Jan. 8, 1940, and the results are represented in figure 1 for comparison with the previous test. The blood cholesterol concentration on Jan. 9, 1940, was 227 mg.% and on May 31, 1940, was 250 mg.%.

Psychiatric re-examination (by Jacob Kasanin, M.D., May 21, 1940). "A cheerful, optimistic young woman who felt that she would be able to go back to work soon, and that she was her normal self again. She experimented with going out and doing whatever she pleased, and found that her relations with people had become pleasant and casual, and even if she did indulge in a certain amount of intimacy and sex relationship these did not cause any undue degree of anxiety such as she used to experience during her illness."

DISCUSSION

This patient presented all the symptoms and signs which are characteristic of the chromaffin in tumors of the adrenal gland, better known as phaeochromocytomas. The hypertensive paroxysms were reproduced by massaging the palpable abdominal mass. Notwithstanding this relatively large mass, intravenous pyelograms did not conclusively demonstrate the tumor. Retrograde pyelograms showed that the upper calices of the right kidney were displaced downward by a tumor mass which did not in itself involve these calices or the pelvis. These changes were sufficient to localize the tumor.

It is evident that intravenous pyelograms should be the first special diagnostic investigation; however, negative findings by this method do not exclude the possibility of a tumor. It must be borne in mind that if a diagnosis can be made with this technic further studies should not be attempted because of danger to the patient. However, retrograde pyelography is indicated in the presence of typical paroxysms with a negative physical examination of the abdomen and an unsatisfactory or highly questionable result from intravenous pyelograms. In the rare instances in which the usual roentgen-pyelographic procedures do not demonstrate the presence of a tumor, a perirenal insufflation, although hazardous (35), may prove valuable.

In interpreting the roentgenologic picture, it is important to differentiate this extrarenal tumor from an intrarenal tumor. This differentiation depends on the presence of a tumor large enough first, to deform the pelvis or calices of the kidney, second, to displace the kidney downward, or third, to rotate the kidney. Intrarenal tumors usually show evidence of destruction of the pelvis or calices; however, the findings mentioned sometimes may be simulated by a hypernephroma, adenoma, or solitary cyst of the kidney, or by other adrenal tumors; but in these instances the typical history will not be present.

It is important to remember that a phaeochromocytoma may be present and not be demonstrated by any of the procedures mentioned. If a patient presents a history characterized by paroxysms of hypertension, surgical exploration is indicated even though the tumor cannot be localized. The occasional origin of these tumors from the extra-adrenal chromaffin tissue is noted in the table, and has been discussed in detail (2). The simultaneous bilateral renal exploration described by Young is probably the operative procedure of choice, and with it, it is advisable that the preoperative and postoperative medication to be discussed should be carried out. If this simultaneous bilateral operation is not desired it is suggested that the right side be explored first. In one instance, the uninvolved adrenal hypertrophied and was mistaken for the tumor, with disastrous results following its removal (4). This physiologic alteration if present must be recognized so that the adrenal gland upon which life is dependent will not be disturbed. Absence of the opposite adrenal, while extremely rare (36), must be considered whenever surgical intervention on the adrenal gland is contemplated.

The hypertensive crisis that occurs in many cases when the operation is begun, and the collapse which follows when the tumor is removed, are difficult to control at the present time, and the influencing factors are not readily evident. The administration of amyl nitrite in *cases 4* and *21*, and in the case of Labbe et al. (37) influenced the usual paroxysm; longer-acting related compounds may aggravate the collapse appearing on extirpation of the tumor. Ergotamine controlled the paroxysms for a short time in our case, finally becoming ineffective. It was not tested during the operatively-induced paroxysm. Piperido-methyl-3-benzo-dioxane (38), a specific antagonist of epinephrin, has not had clinical trial in this specific condition. The type of anesthesia has little influence in producing or modifying the crisis and subsequent collapse, as indicated by the reported cases. Excitement and manipulation of the patient in preparation for operation may be playing a greater part than is suspected. If this is true, all preparatory procedures should be limited to those absolutely necessary and the tumor should be expeditiously removed.

Before preoperative and postoperative treatment are discussed, it is necessary to understand the physiologic changes produced by a phaeochromocytoma.

These tumor cells have been shown in numerous instances to contain, and undoubtedly produce, an epinephrin-like pressor substance. Histologic examination of these tumors usually shows that they consist almost entirely of medullary tissue; cortical cells can occasionally be found in small groups. While these cortical cells may be widely dispersed, presumably they are still functioning. In one instance, as mentioned previously (4), the opposite adrenal seemed enlarged, which may have been a compensatory cortical hypertrophy, but this does not always occur. There is a possibility that because of a superabundance of hyperactive medullary tissue in the tumor, the chromaffin tissue in the other adrenal and in the remainder of the body may be functionally depressed. On removal of the tumor the excess pressor substances are suddenly withdrawn, thus placing a demand for both medullary and cortical hormones on the remaining gland which may not be prepared for this emergency.

This explanation accounts for the fall in blood pressure on removal of the tumor, and the appearance of a condition which has been termed "shock" in this report. The immediate fall in blood pressure is probably due to extirpation of the pressor-producing tumor tissue, with the withdrawal of epinephrin or related substances from arterioles which may have become accustomed to relatively high concentrations of these materials. The prolonged hypotension and collapse noted in many cases probably results from a superimposed temporary deficiency of both cortical and medullary substances. The short but dramatic responses of this condition to epinephrin seems to differentiate it from surgical shock. The loss of venous or capillary tone in the latter does not respond to epinephrin. It is also possible that operative damage to nerve plexuses may be influencing the prolonged collapse.

The rationale for the pre- and postoperative treatment used in this case is evident. To obviate the temporary cortical deficiency a high salt diet together with desoxycorticosterone acetate was given preoperatively. To combat the immediate collapse during operation when the tumor was removed (fig. 5) the patient was given epinephrin intravenously and subcutaneously, and intramuscularly in oil, along with additional adrenal cortex extract and desoxycorticosterone acetate. The administration of blood and fluids with added epinephrin was also started through the continuous intravenous drip.

The similarity of adrenal cortical deficiency and some phases of surgical shock (39) indicated that adrenal cortical therapy may be a valuable adjunct in prevention and in the treatment of the latter (40). It is especially important in any instance where the adrenal glands are subjected to operation, for here it is possible to have a temporary interference with cortical function in addition to surgical shock. When these two factors are present the accepted procedures for the treatment of shock do not seem to be adequate. This was shown in the 4 cases that did not survive, and in the three instances (*cases 21, 27* and *29*) where the shock showed a very definite improvement following the administration of cortical hormone. The use of the synthetic cortical hormone has been suggested when surgical intervention in adrenal cortical neoplasms is contemplated, for it was found that atrophy of the contralateral adrenal occurred in 21 of 34 reported cases (41). In our case we found it necessary to give large doses of both adrenal cortex extract and desoxycorticosterone acetate. We feel that these compounds played an important role in the immediate postoperative condition by maintaining the blood electrolytes. Undue prolonged shock has been noted when an adrenal containing a cortical tumor has been removed (42); this manifestation of shock probably differs from that seen in phaeochromocytomas in that in the former there has not been a sudden modification of a lesion producing a hyperepinephrinism.

SUMMARY

A case of phaeochromocytoma involving the right adrenal gland, and having a typical history of hypertensive paroxysms, a palpable mass, and characteristic roentgenograms, in which surgical removal was successful is discussed in detail. A remarkable feature is the progressive disappearance of the severe changes in the optic fundi and a return to normal of the dextrose tolerance test after removal of the tumor. The literature has been reviewed with special emphasis upon the localization of the tumor, the measures used in preoperative and postoperative treatment and the present status of the surgically cured cases. It was found necessary to use epinephrin in addition to the usual treatment for postoperative shock, especially to combat the sudden collapse during and immediately following surgery. The use of desoxycorticosterone acetate and adrenal cortex extract definitely seemed to lessen the severe postoperative hypotensive crisis. A rationale has been presented as a basis for the preoperative and postoperative use of these two substances.

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REFERENCES

1. Belt, A. E., and T. O. Powell: *Surg. Gynec. & Obst.* 59: 9. 1934.
2. Howard, J. E., and W. H. Barker: *Bull. Johns Hopkins Hosp.* 61: 371. 1937.
3. MacKenzie, D. W., and D. McEachern: *Trans. Am. Asso. G.-U. Surgeons* 31: 127. 1938.

4. Volhard, F.: Handb. d. inn. Med. von v. Bergman u. Staehelin. 2nd Edition. Vol. 6, pt. 2, 1272, Berlin, 1931.
5. Hatieganu, J., H. Moga and P. Radu: *Bull Acad. de med. de Roumanie* 4: 179. 1939.
6. Masson, P., and J. F. Martin: *Bull. A. franc. p. l'etude de Cancer* 12: 135. 1923.
7. Mayo, C. H.: *J.A.M.A.* 89: 1047. 1927.
8. von der Muhll, R.: Thesé de doct. Lausanne, 1928.
9. Pincoffs, M. C.: *Trans. Asso. Am. Phys.* 44: 295. 1929.
10. Shipley, A. M.: *Ann. Surg.* 90: 742. 1929.
11. Porter, M. F., and M. F. Porter, Jr.: *Surg. Gynec. & Obst.* 50: 160. 1930.
12. Lazarus, J. A., and A. A. Eisenberg: *J. Urol.* 27: 1. 1932.
13. Suermondt, W. F.: *Zentralb. f. Chir.* 61: 70. 1934.
14. Bauer, J., and R. Leriche: *Presse med.* 42: 1385. 1934.
15. Coller, F. A., H. Field, Jr., and T. M. Durant: *Arch. Surg.* 28: 1135. 1934.
16. Van Goidsenhoven, F., and R. Appelmans: *Bull. Acad. Roy. de med. de Belg.* 14: 672. 1934.
17. Kalk, H.: *Klin. Wchnschr.* 13: 613. 1934.
18. Büchner, F.: *Klin. Wchnschr.* 13: 617. 1934.
19. McKenna, C. M., and L. E. Hines: *J. Urol.* 34: 93. 1935.
20. Kelly, H. M., M. C. Piper, R. M. Wilder and W. Watters: *Proc. Staff Meet. Mayo. Clinic* 11: 65. 1936.
21. Landau, A., L. Paskiewicz, Zd. Slawinski and E. Steffen, Jr.: *Rev. belge de sc. Med.* 8: 330. 1936.
22. Burgess, A. M., G. W. Waterman and F. B. Cutts: *Arch. Int. Med.* 58: 433. 1936.
23. Beer, E., F. H. King and M. Prinzmetal: *Ann. Surg.* 106: 85. 1937.
24. Pincoffs, M. C.: Quoted by Howard and Barker (2).
25. Borch-Johnson, E.: *Acta Chir. Scandinav.* 80: 171. 1937.
26. Borras, P. E., and M. M. Mota: *La Semana Med.* 1: 990. 1938.
27. Binger, M. W., and W. McK. Craig: *Proc. Staff Meet. Mayo Clin.* 13: 17. 1938.
28. Brunschwig, A., E. Humphreys and N. Roome: *Surgery* 4: 361. 1938.
29. Nuzum, F. R., and J. W. Dalton: *Am. Heart J.* 16: 643. 1938.
30. Holst, E. J.: *Acta Med. Scandinav.* 94: 510. 1938.
31. Strömbeck, J. P., and T. P. Hedberg: *Acta Chir. Scandinav.* 82: 177. 1939.
32. Van Epps, E. F., O. R. Hyndman and J. A. Greene: *Arch. Int. Med.* 65: 1123. 1940.
33. Eloesser, L.: Personal communication.
34. Rabin, C. B.: *Arch. Pathol.* 7: 228. 1929.
35. Weyrauch, H. M., Jr.: *J.A.M.A.* 114: 652. 1940.
36. Lukens, F. D. W., H. F. Flippin and P. M. Thigpen: *A. J. Med. Sci.* 193: 812. 1937.
37. Labbe, M., J. Tivel and Doumer: *Bull. et mem. de l. soc. med. des hop. de Paris* 46: 982. 1922.
38. Katz, L. N., and L. Friedberg: *Am. J. Physiol.* 127: 27. 1939.
39. Harrop, G. A., and A. Weinstein: *J. Exper. Med.* 57: 305. 1933.
40. Perla, D., D. G. Freiman, M. Sandberg and S. S. Greenberg: *Proc. Soc. Exper. Biol. & Med.* 43: 397. 1940.
41. Wienberg, T.: *Arch. Pathol.* 29: 862. 1940.
42. Eliason, E. L.: *Internat. Clinics* 48: vol. II, 221, 1938.

ADDENDUM

After completion of this manuscript and the tables, Brunschwig and Humphries reported (*J.A.M.A.* 115: 355. 1940) the successful surgical removal of a phaeochromocytoma in a 43-year-old female, in whom the diagnosis was made on clinical grounds without the aid of roentgenographic studies. A tumor 4 cm. in diameter, weighing 13.5 gm., was found in the right adrenal gland; surgical manipulation of this tumor produced an hypertensive paroxysm. The blood pressure fell to 100 systolic and 60 diastolic on conclusion of the operation, but this drop was not classified as "shock," and did not require the administration of epinephrin or adrenal cortex hormone.

ADRENAL MEDULLARY TUMOR

STUDY OF A CHROMAFFIN CELL TUMOR OF THE ADRENAL

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PERHAPS lack of physiologic studies undertaken on tissues removed at operation and autopsy has kept knowledge of the functional aspects of endocrine tumors imperfectly developed. Such studies even today are a rarity. This fact prompts publication of work in which we were fortunately able to carry out extract studies on a medullary chromaffin cell tumor secured very shortly after death. These dark brown pigmented tumors, usually of relatively small size, have been described (1, 2). Their comparative morphology is given by Peyron (3); recent summaries are those of Rabin (4) and of Lewis and Geschickter (5). The clinical aspects were reviewed in 1937 (6).

CASE ABSTRACT AND STUDY

Clinical. The present case is that of a 40-year-old female whose symptoms were those of well-circumscribed attacks of hypertension usually accorded these patients. She had noticed their onset with nervousness, flushing, and sweats a number of years previously. In the past six months, dyspnea, orthopnea, and palpation had been marked. Several such attacks occurred each day, apparently brought on by eating or pressure on the tumor. During one of the attacks the blood pressure rose to 290/185. There was a palpable mass the size of a grapefruit in the left upper abdominal quadrant on which any pressure or palpation caused a great increase in blood pressure. The patient died during one of the attacks.

Necropsy. The autopsy was performed 30 minutes after death. It was noted that the body was that of a well-formed white female of about the age given; the nourishment was good. The skin was clear, light tan, showing no scars or blemishes except for striae of child bearing in the lower abdomen. There was no edema or jaundice. The body measured 168 cm. in length and weighed 57 kg. Rigor mortis had not yet set in. There was a small conjunctival hemorrhage near the limbus of the left eye. The head was covered with thick black hair.

The serosal coats of the thoracic and abdominal cavities were smooth and moist. The heart was distinctly hypertrophied; it weighed 460 gm. The left ventricular myocardium was thickened but showed no scars. The tricuspid, pulmonary, and mitral valves were normal. There was one yellow plaque in the base of the mitral valve. The aortic cusps also showed a few little sclerotic plaques at their bases. There were a few early fat deposits in the aorta above the valve. The coats of the coronaries seemed a little thicker than usual. The lungs were everywhere air-containing. The mucosa of the trachea was injected. The Malpighian bodies were very distinctly visible; the pulp is dark purple. The liver and pancreas showed no gross lesion. The esophagus, stomach and duodenum were quite contracted. The remainder of the small and the large intestine showed no abnormalities. The uterus was normal in size and placement. There was a small fresh corpus luteum in the right ovary. The external surface of the kidneys showed no scarring. There was a depression in the outer upper pole of the left kidney caused by compression from the tumor in this region.

The right adrenal showed a number of small adenomatous nodules on its cut surface. It measured 6.5 × 4 × 0.4 cm. What remained of the left adrenal was intimately connected with the large tumor growing from its superior aspect. The tumor from the left adrenal was entirely encapsulated; its outer surface was lobular. It measured 13 × 12 × 8 cm. and weighed 560 gm. The tumor on section showed a great deal of hemorrhage and necrosis which in the outer portion was cystic; the better preserved areas were a curious dark yellow. The tumor was soft and was made up of a series of lobules which were very indefinitely outlined without much connective tissue. At the inferior pole one could still see adrenal closely applied to the surface of the tumor. Just between this and the tumor proper there was a good-sized vessel which was apparently one of the large adrenal veins. The remaining left adrenal tissue appeared in the form of cortical tissue which was bright yellow with a brownish inner zone. At the inferior pole there was a much dilated, thickened vein containing a thrombus. The surface of the thrombus seemed fresh; the lower layers were dense and partly hyaline. In the neighborhood of this vein there were several little nodules of accessory cortical adrenal tissue. Slices of the tumor when placed in Zenker's solution turned dark brown, showing the medullary chromaffin nature of the tumor. No metastases were found.

Microscopic. The tumor was composed of masses of fairly uniform cells which were elongated with rather pale-staining nuclei. Some had greatly enlarged nuclei and were themselves very large. There were in places small accumulations of lymphoid cells in the framework of the tumor. The tumor cells were finely pigmented with a brown pigment. A microscopic section of tumor is shown in figure 1. Study of the tumor cells using high magnification (1395 ×) and a special cytoplasm stain showed them to contain heavy granules. These were equally distributed in the

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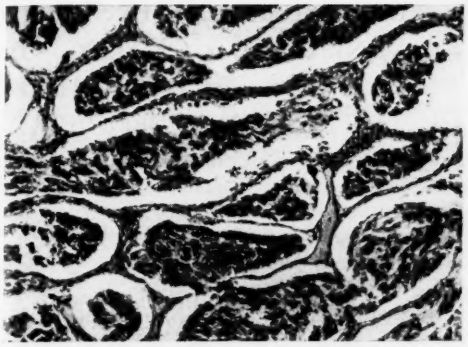

Fig. 1. ×150. Showing the grouping of the tumor cells by fibrous septa, and the general microstructure of the tumor.

cytoplasm and appeared not unlike the Nissl's substance in nerve cells.[1]

The right adrenal was normal except that medullary cells seem shrunken and some of them contain pyknotic nuclei. In the kidneys there was moderate arteriosclerosis in a rare arteriole. The parenchyma of the pancreas, liver and spleen was normal; rarely an arteriole showed moderate arteriosclerosis. Abundant colloid was present in the acini of the thyroid. In the heart myofibrillae were hypertrophied; no scars were found.

Physiologic Study of Tumor

Immediately on removing the tumor, it was cut in two sections, and one of these was ice boxed for pharmacologic study. The half to be thus studied remained in the ice box for three hours at which time it was removed and an extract made of it as follows. Fifty grams of the tumor tissue were taken from the superior pole of the tumor. This was ground in a mortar with 100 cc. of ethyl alcohol, made faintly acid with acetic acid, and allowed to stand overnight in the ice chest. The alcohol was evaporated by placing in front of a fan, the residuum being put in water solution. The resulting solution being extracted was finally made to 15 cc. This extract when tested with ferric chloride gave a strongly positive deep green color reaction for adrenalin (presumptive).

The injections were made as follows. The animal used was a female cat, non-pregnant, weighing 2.78 kg. Under luminal anesthesia, smoked drum recordings of the blood pressure were made.

(1) Injection of 0.2 cc. of adrenalin, 1:100,000
(2) 0.4 cc. of 1:100,000
(3) Injection of adrenal tumor extract (from the 15 cc. of water extract)—0.2 cc. diluted 1:25,000
(4) One-half of (3)
(5) 0.1 cc. of (3) diluted 1:1
(6) 0.1 cc. of (3) diluted 1:1
(7) 0.4 cc. of 1:100,000 adrenalin

[1] I am indebted to Dr. W. G. MacCallum, particularly for the stains used in the micro-sections. The stain is combined phosphotungstic acid and polychrome methylene blue.

For (1), (2), and (7) Parke, Davis, & Co. adrenalin solution of 1:1,000 solution, diluted as indicated, was used.

We may take for granted that similar quantities of adrenalin will give similar reactions in blood pressure. The reactions obtained from injections (4) and (7) gave similar curves. Hence the 15 cc. of extract from 50 gm. of tumor tissue is calculated to have contained 0.6 mg. of adrenalin. The tumor weighed 560 gm. Although fairly homogeneous and the tissue for extraction was chosen from a variety of places, we may consider that if the whole tumor had been extracted, it would have contained 67.2 mg. of adrenalin. However, there were hemorrhagic areas so there was probably actually less.

To summarize we may say that normal adrenals contain from 8 to 10 mg. of adrenalin (7), and if this tumor contained 67.2 mg., the quantity being put into the blood stream was surely greater than normal.

DISCUSSION

The present case again brings up the problem of secretion of substances by tumor tissue, and while not conclusive, does lead one to believe that such is probably of common occurrence. The present tumor was not a highly anaplastic one. It is interesting to speculate as to the degree of anaplasticity which may occur and yet the tumor show secretory activity. Quantitatively in this and other cases reported the amount of adrenalin has been high (8, 9, 10).

Clinically the patient showed evidence of hyperadrenalin secretion. We cannot be completely certain that the substance from the tumor was adrenalin, though the studies are most suggestive. Nor can we be certain of the quantities of the substance secreted though, as mentioned, clinically we would suspect large quantities. The extraction studies point to the presence of a large amount of adrenalin actually in the tumor (67.2 mg.). The average amount recoverable from both adrenals is about 8 mg. (7).

REFERENCES

1. Berdez: *Arch. de méd. expér. et d'anat. path., Paris* 4: 412. 1892.
2. Laignel-Lavastine and Aubertin: *Arch. de méd. expér. et d'anat. path.* 20: 818. 1908.
3. Peyron, A.: *Bull. Assoc. franç. p. l'étude Cancer* 19: 618. 1930.
4. Rabin, C. B.: *Arch. Path.* 7: 228. 1929.
5. Lewis, D., and C. F. Geschickter: *Arch. Surg.* 28: 16. 1934.
6. Howard, J. E., and W. H. Barker: *Bull. Johns Hopkins Hosp.* 61: 371. 1937.
7. Grollman, A.: The Adrenals. Williams & Wilkins Co., Baltimore, 1936. 410 pp.
8. Labbé, M. Azérad, and Violle: *Bull. et mém. Soc. méd. des hôp. de Paris*, 53: 952. 1929.
9. Kalk, H.: *Klin. Wchnschr.* 13: 613. 1934.
10. Kelly, H. M., M. C. Piper, R. M. Wilder and W. Walters: *Proc. Staff Meet. Mayo Clin.* 11: 65, 1936.

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ORAL THERAPY OF TESTICULAR DEFICIENCY

METHYL TESTOSTERONE ADMINISTERED ORALLY TO PATIENTS WITH MARKED TESTICULAR DEFICIENCY[1]

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SEARCH for a potent testicular hormone has been rewarded with the discovery and development of testosterone and related androgenic steroids. The effectiveness of the various preparations of testosterone, administered by injection, by pellet implantation and by inunction has been attested by numerous observers (1, 2, 3).

All methods of testosterone treatment have produced striking responses in various metabolic activities as well as in the sexual functions. However, testosterone and testosterone propionate are only slightly active when given by mouth.

More recently the introduction of methyl testosterone for oral administration has produced encouraging results. This method gives promise of becoming a most acceptable form of treatment.

During the past 9 months 12 patients including 3 castrates, 5 eunuchoids and 4 patients with nervous symptoms and partial impotence have received methyl testosterone by mouth.

The maximal oral dose was 100 mg. daily, given in 4 doses, although 50 mg. daily was ample in the average patient. Every dose is taken on a thoroughly empty stomach with one-half glass of hot water to insure maximal absorption. Comparing the effects obtained in patients treated by the other routes of administration it was found that from 4 to 6 times the injection or inunction dose is required.

After Ruzicka (4) and Butenandt (5) concomitantly developed a method for the breaking down of sterols, a series of compounds of testosterone became relatively easily accessible. Among these preparations, including methyl testosterone, there exist marked variations in effects in different species, variations in effects on various organs in different species and variations between the ratios of its activities on different organs in the same species, depending on the mode of administration.

The first inkling as to the possibilities of methyl testosterone for oral administration was obtained in 1938 by Miescher and Tschopp (6) who found that the methyl derivative retains its activity, when given by mouth to castrated rats, much better than does testosterone. In rats, the required oral dose was found to be only 2½ times the injection dose. Moreover methyl testosterone was shown to be more effective than any of the other androgens tested and between 2 and 3 times more effective than free testosterone in peroral use.

Emmens and Parkes repeated the experiments on capons with less decisive results. The dose of free testosterone required by mouth to produce a given comb growth increase was 30 times that required by injection whereas with methyl testosterone, the ratio of oral to injection dose was only 8 to 1. The superiority of methyl testosterone as an oral agent was much more clearly demonstrated when Emmens and Parkes repeated the work of Miescher and Tschopp, in mammalian tests (7).

Foss (8) was the first to report the results of the ingestion of methyl testosterone in man. Six patients were treated, 3 males including a castrate 38 years of age, 2 prepuberal boys, ages 10 and 11 with hypogonadism, and 3 women with dysmenorrhea. Remarkable results were obtained in all 3 males, the castrate being relieved of symptoms after about 3 days, followed by prompt development of full potency. In the 2 boys, the beneficial effects were equally gratifying; rapid development of the penis, gain in weight, and improvement in general well-being occurred.

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Explanation for the increased potency of methyl testosterone over the other androgens in oral administration has brought out two theories. Miescher and Tschopp suggest the possibility that the presence of the methyl group adjacent to the active androgenic hydroxyl group possibly protects the latter by "stearic hindrance" from a fermentative action in the intestinal tract. Biskind (9), after considerable animal experimentation, found that methyl testosterone like testosterone propionate, does not exert its specific effect on the genital organs of castrate male rats when implanted in pellet form in the spleen. When the pellet is placed in the transplanted spleen with the splenic vessels ligated, thereby shunting its circulation from the portal into the systemic circulation, enough is absorbed to be capable of exerting a specific androgenic action. As both androgens appear to be destroyed in the liver, it is suggested that the differences in the specific effects of these two substances, when administered orally, may be due to different routes of absorption from the intestinal tract, that is, through the lacteals and lymphatics rather than by way of the portal circulation. This, he believes to be a more likely explanation than a lesser destruction of methyl testosterone by intestinal ferments.

To attain all of the desired beneficial effects of testosterone administration, testicular deficiency must exist. In the normal individual, the sexual functions may be depressed by the administration of any form of testosterone (fig. 1). This undesirable side effect is occasionally observed in patients who have received testosterone in the treatment of infertility.

In the presence of deficiency, methyl testosterone perorally has produced all of the desired effects that other routes of administration have produced.

In our patients, the changes in the urinary androgenic output, water balance and the creatinine retention test, gave added proof to the clinical evidence of utilization by the body.

Among the various types of patients to whom testosterone has been administered, castrates are the most amenable, are most definitely benefited, and show the lowest threshold of response. Symptoms are relieved with a smaller dose than in any other type of patient. Their loss of libido and lack of sexual power ordinarily gives them no concern. They appreciate relief from mental depression and anxiety, and from general muscular weakness, and fatigability. Prompt relief from these symptoms is brought about after any of the routes of administration and with surprisingly small doses of testosterone. The patients are changed from shy, apprehensive, depressed individuals, to hopeful, cheerful, interested social beings.

In two alcoholic castrates very definite diminution in craving for alcohol occurred each time treatment was resumed.

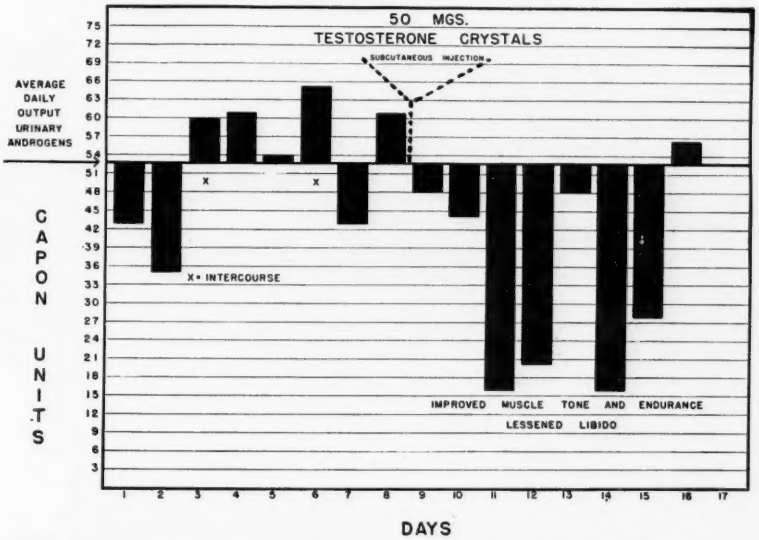

Fig. 1. Normal man, age 37 years. During the first 8 days of observation the daily urinary output of androgens averaged 52.6 c. u. This was considered the mean level for this patient and is indicated by the base line. On the 8th day 50 mg. of testosterone crystals was injected intramuscularly. There followed a marked drop in androgenic output and a definite loss of libido which persisted for one week. An interesting side effect occurred in the appearance of increased muscular tone and a lessened tendency to fatigue.

When the dosage is increased and the threshold for sexual manifestations is obtained, sexual desire and potency appear. The atrophic prostate gland gradually increases in size and the facial hair becomes coarse and grows rapidly.

groups in whom testosterone is administered. Hesser, Langworthy, and Vest (12) have observed beneficial results in 2 male patients suffering with myotonia atrophica following treatment with testosterone.

In our efforts to obtain objective measurements to

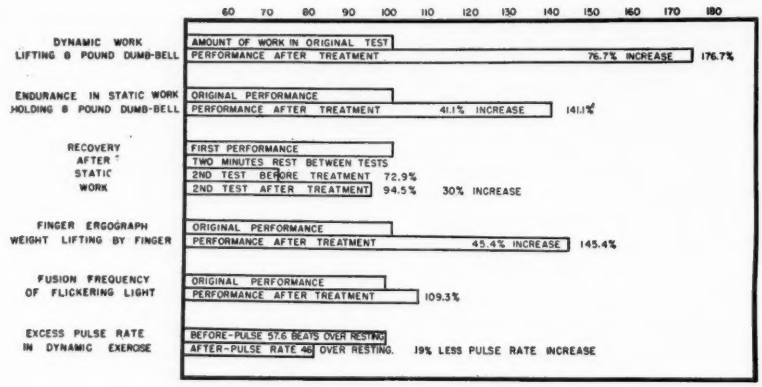

Fig. 2. Effects on the nervous and muscular systems of oral administration of 100 mg. of methyl testosterone daily. Measurements were made on 4 patients—two castrates and two typical eunuchoids. The average percentage gain of the 4 patients is recorded for each test. Measurements were repeated twice before institution of therapy and two tests were made after 3 weeks of treatment.

Edema is apt to develop in the lower extremities when the castrate is placed on a large dosage of methyl testosterone and especially when an initial large dose is given. This by-effect which is easily overcome by regulation of dosage has been noted by Thompson and Heckel (11) and others after the administration of testosterone in various forms.

When this reaction occurs the McClure-Aldrich (10) test measuring the absorption time of intradermal injection of normal saline solution is accelerated. This action of testosterone resembles that of the closely related adrenal cortex hormone. The adrenal cortex hormone has been given to castrates without benefit, and vice versa, testosterone to patients with Addison's disease with negligible effect. While these two closely related steroids are not interchangeable for some specific effects, they have a common physiological effect in influencing the water balance in the tissues. This known effect of the steroidal hormones on the water balance explains the phenomenon of edema with its attendant changes in the McClure-Aldrich test and the creatinine utilization test. It may also explain the behavior of the alcoholic under treatment.

Concomitantly with the change in the mental state, all patients register their appreciation of a definite change in the muscular system evidenced by the hand-grip, ability to walk more rapidly and with greater endurance. This has been the most consistent subjective result not only in castrates, but in all

supplement the oft repeated subjective record of the patient, pertaining to increased endurance, six tests for performance in exercise and in staying power were carried out.

Two castrates and two eunuchoids were twice tested with various exercise and endurance performances after a period of rest of at least 4 weeks from treatment. The tests were repeated after 3 weeks of treatment with 100 mg. daily of methyl testosterone administered orally. The results serve to confirm the prevailing view that sexual hormones are related to the metabolism of muscle and to creatinine balance.

The group tested includes a castrate, 45 years of age who had previously received testosterone ointment and propionate injections; another castrate, 35 years of age who had received ointment, propionate injections and testicular transplants; a eunuchoid, 20 years of age who had received gonadotropins, testosterone propionate injections and testosterone ointment; and a eunuchoid 27 years of age who had received ointment, injections and pellet implantations of testosterone. In these 4 patients the following significant results were obtained.

(*a*) Endurance in the dynamic work of weight lifting is greatly increased as measured by the time and amount of work performed before development of fatigue.

(*b*) Endurance in static work consisting in holding an 8-pound dumbbell with outstretched arm is increased to a lesser degree, but is also definitely increased.

(*c*) Recovery in static work, that is, the ability to repeat exercises after a given interval of rest, is definitely increased.

(*d*) Endurance or performance with the finger ergometer is increased from 20% to 40%.

(*e*) Muscle power in the ability to carry out a single effort is only slightly increased.

(*f*) The fusion frequency of flickering light is increased from 3 to 7 flashes per second or from 6 to 14% under treatment. This indicates increased resistance of the central nervous system to fatigue. A slow fusion rate of flickering light is typically found in patients with various glandular deficiency diseases, cardiac disease and other exhaustion states (fig. 2).

These measured effects, obtained in the 4 patients with marked hypogonadism, were accompanied with beneficial effects on the nervous system and sexual power.

A similar good effect was obtained in the other castrate and three eunuchoids in the series. The remaining patients of the series receiving oral treatment were 4 men, ranging in age from 53 to 67 years, who were complaining of various nervous symptoms, exhaustion and impotency. The response in these patients was far less striking, although all were improved in varying degrees. All 12 patients in the series had previously received treatment with one or more different routes of administration of testosterone. In comparing the different routes of administration, oral administration, both in objective and subjective effects, compared favorably with any of the other methods.

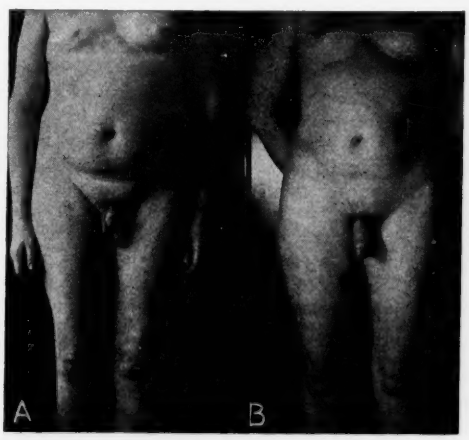

Fig. 3. EUNUCHOID, AGE 47. *A*, Before treatment, 1/22/40. Height 74 in.; arm span 76 in. Both testes descended but atrophic; bilateral orchitis. Married 13 years: partially impotent first 8, impotent for last 5 years.
B. After treatment 6/10/40. Methyl testosterone was administered orally (50 to 100 mg. daily) continuously.

It is possible that these proven changes in skeletal muscle power may well be duplicated in the bladder detrusor musculature and explain the improved emptying power which often promptly follows treatment with testosterone in patients with prostatism. Lippross (13) measured cystometrically the bladder tonus in elderly men before and after treatment with the male hormone and noted definite improvement in the emptying power.

In this connection the work of Papanicolaou and Falk (14) is interesting. Their experiments with the administration of testosterone propionate to castrated male, and spayed as well as normal adult female guinea pigs resulted in definite hypertrophy of the musculature throughout the body. The experiments were repeated for prolonged periods with progesterone and estrogen without any effect demonstrable on the voluntary muscles. If the testosterone was combined with either progesterone or estrogen a general muscular hypertrophy again resulted.

The effects of oral administration of methyl testosterone in human testicular deficiencies closely parallel these results on the muscular system.

All of the various routes of administration of the various testosterone preparations may be duplicated by the oral administration of methyl testosterone and without some of the objectionable features attendant upon the other methods (fig. 3).

It is interesting to note that the frequent occurrence of undesirable side effects observed with oral use of stilbestrol is lacking following the oral administration of methyl testosterone. No gastric irritation or any other undesirable reaction was obtained in the 12 patients treated, except in one eunuchoid who experienced a moderate degree of gastric irritation which was readily controlled with an alkaline mixture.

The choice of method for the administration of testosterone preparations in testicular deficiency depends on the following.

(*a*) The physiological response in the individual patient to the particular form of treatment.

(*b*) The availability of the different forms of testosterone as influenced by the patient's location, economic status, etc.

(*c*) The attitude and cooperation of the patient to the particular method of treatment.

CONCLUSIONS

Methyl testosterone is practical and efficacious in oral administration.

In patients with marked testicular deficiency, who were previously treated with testosterone by various routes, it duplicated and maintained all of the beneficial effects.

The ill-effects are negligible—slight gastric irrita-

tion was the only unpleasant by-effect observed.

Approximately four to six times the inunction and injection dosage is required.

If the cost of manufacture of methyl testosterone in large quantities is not excessive, the oral administration may become most acceptable and replace in large measure the other methods.

Simplicity of administration, even distribution of dosage and convenience to the patient are the chief advantages over the other routes of application.

Its dispensation should be limited to physician's prescriptions as its indiscriminate use may have undesirable results.

My thanks are due to Doctor Ernst Simonson, formerly professor of physiology, University of Frankfort for the tests of fatigue; to Professor A. Bock, to Charles Neterval of the Department of Biochemistry, Marquette University School of Medicine, for technical help and advice, and to Doctor Max Gilbert of the Research Department of the Schering Corporation for the supplies of oreton ampules, oreton toplicators, and oreton-M tablets (methyl testosterone).

REFERENCES

1. Kenyon, A. T., I. Sandiford, A. H. Bryan, K. Knowlton and F. C. Koch: *Proc. Soc. Exper. Biol. & Med.* 37: 683. 1937.
2. Vest, S. A., Jr., and J. E. Howard: *J. Urol.* 40: 154. 1938.
3. Kearns, W. M.: *J.A.M.A.* 112: 2255. 1939.
4. Ruzicka, L., M. W. Goldberg, J. Meyer, H. Brungger and E. Eichenberger: *Helv. Chim. Act.* 17: 1935. 1934.
5. Butenandt, A., and G. Hanisch: *Ztschr. f. physiol. Chem.* 237: 89. 1935.
6. Miescher, K., and E. Tschopp: *Schweiz. Med. Wchnschr.* 68: 1258. 1938.
7. Emmens, C. W., and A. S. Parkes: *J. Endocrinol.* 1: 323. 1939.
8. Foss, G. L.: *Brit. M. J.* 2: 11. 1939.
9. Biskind, G.: *Bull. Johns Hopkins Hosp.* 65: 212. 1939.
10. Hopps, H. C., and F. Christopher: *Surg., Gynec., & Obst.* 69: 637. 1939.
11. Thompson, W. O., and N. J. Heckel: *J.A.M.A.* 113: 2124. 1939.
12. Hesser, F. H., O. O. Langworthy and S. A. Vest: *Endocrinology* 26: 241. 1940.
13. Lippross, O.: *Muenchen. Med. Wchnschr.* 85: 1668. 1938.
14. Papanicolaou, G. and E. Falk: *Science* 87: 238. 1938.

THERAPY IN MALE HYPOGONADISM

TESTOSTERONE PROPIONATE INUNCTION AND METHYL TESTOSTERONE ORALLY. CASE REPORT

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THE SUCCESSFUL TREATMENT of male hypogonadism by means of injections of testosterone propionate has been repeatedly demonstrated (1–7). Experience regarding the applicability of two other routes of administration, namely, by inunction (8, 9) and orally (10) has been very limited. It appeared, therefore, pertinent to present the following case report on the effectiveness in a hypogonad male of *a*) testosterone propionate by inunction and, *b*) methyl testosterone by mouth.[1]

P. W. (age 19 years) was first seen in January, 1940, complaining of genital underdevelopment. The family history was of no obvious significance and the past history presented the usual childhood illnesses in a mild form (measles whooping cough, mumps) occurring before 10 years of age. Hypogenitalism was first noted about this time, penis was small and testicles could not be palpated in scrotum. From the age of 10 to 14 years, he suffered from a great deal of nausea, headaches and occasional vomiting. Various endocrine products were administered, including pituitary-like sex principles, in adequate doses, until two years ago. Several pubic hairs appeared at 16 years of age, none since. Erections have occurred only a few times a year for the past several years. There were no emissions, the boy was very intelligent and acutely aware of his inadequacies. Ambitious and imaginative, he was handicapped by a constant feeling of exhaustion, in spite of which he was able to finish high school with good grades, enter Junior College and contribute to his own financial support.

Physical examination revealed a male 19 years of age, appearing much younger than his years, height 66.4 in., weight 140 lb., of a typical hypogonad configuration with long fingers and lower extremities. The body was fleshy rather than muscular with a feminine tendency in weight distribution. The voice was high-pitched and boyish. Facial skin was of a grayish, pallid hue with dark "hangover" type of discoloration under the eyes. Lips were bright red, dehydrated. Body skin was dry, soft, velvety and devoid of any hair. Facial hair was not present and there were only a few stray axillary and pubic hairs. The penis was button-like, one-half inch in length and less in diameter. The scrotum was pale, velvety, measuring one and one-half inches in diameter. Testes could not be found in the scrotum, the left was soft, less than one-half inch in length and in the external inguinal ring. The prostate was barely palpable. The physical examination results were otherwise normal. Blood pressure was 110/65, basal metabolic rate −17% (basal pulse 76, temperature 98.6). Serum cholesterol 200 mg. per 100 cc. Fasting blood sugar 87 mg. and two and one-half hours after a carbohydrate rich breakfast, 100 mg. per 100 cc. The urine was normal. Preformed creatinine excretion was 1,350 mg., creatin 225 mg. (values per 24-hour urine output on a meat free diet). Blood count was R.B.C. 5.6 million, hemoglobin 100%; W.B.C. 6,400 with polynuclears 62%. Wassermann test result was negative. Roentgenogram of the skull revealed cranium of normal thickness. Convolutional markings were normal in their depth and number. No intracranial calcifications or erosions were evident. Sella turcica was open and measured 11.5 × 10 mm. Frontal sinuses were rudimentary in type. Roentgenograms of the hands and knee showed all epiphyses wide open indicating approximately a 4-year delay in closure.

Treatment. Testosterone propionate was rubbed in twice daily (3.5 gm. of ointment containing 7 mg. of testosterone propionate in each application) into the skin of the thigh region and lower abdomen. A 50 gm. tube containing 100 mg. of testosterone propionate was thus consumed per week. An increased vascularity of the penis and scrotum was first noticed within 10 days, reaching its maximum in 4 weeks. The penis enlarged to one and one-half inches, the glans penis increasing to one inch at its widest diameter. The scrotal skin became corrugated, pendulous and of a deep pink coloration. The left testicle became more firm. There was a definite increase in the pubic and axillary hair. Erections occurred several times each

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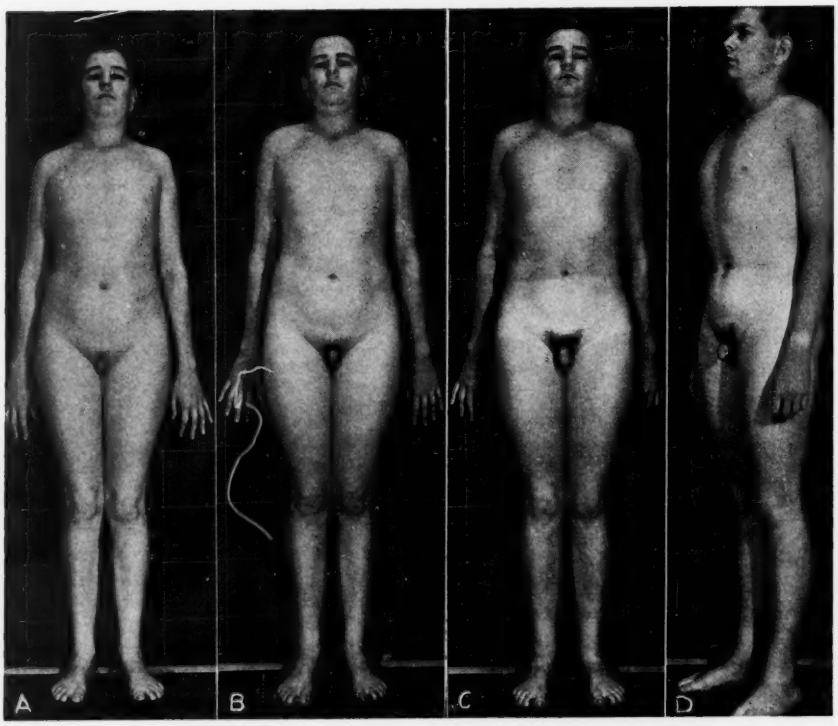
[1] Both products supplied through the courtesy of Ciba Pharmaceutical Products, Summit, New Jersey.



P. W., age 19. The effect of inunction of testosterone propionate (total dose 400 mg.)—A, initial and B, 4 weeks later. C and D, the effect of oral administration of methyl testosterone (total dose 3,600 mg.) 3 months later than B.

week. There were no emissions. There was only little improvement in the fatigability. Treatment was similarly continued for another 8 weeks without evidence of any further change in genitalia. Inunctions were discontinued without noteworthy change other than some loss of the erythema of the genitalia. Methyl testosterone was then administered in the form of 10 mg. tablets, total daily dose of 40 mg. (20 mg. b.i.d. on an empty stomach). A decided congestion of the scrotum and penis was manifest at the end of a week, erections occurring at night and several times daily. Emissions of thin watery material occurred mainly at night. Tendency to masturbation developed for a period of several weeks but was easily controlled. Genital development continued so that at the end of 90 days the penis had enlarged to a length of two and three-fourths inches in relaxation (patient was requested to measure in erection at night which was reported at three and one-half inches) with a circumference of three and one-fourth inches. The scrotum became further corrugated and the prostate enlarged only slightly attaining about one-fifth of normal size. There was a marked appearance of pubic and axillary hair, a downy hirsutism also appeared on the chin and upper lip. The voice began to deepen after the tenth week of treatment and progressed very rapidly to a normal male pitch at the end of the twelfth week. No less remarkable was the improvement in energy and mental outlook. Feeling of unreality and frustration from which he suffered vanished and were superseded by a definite ambition and optimism. During the last two weeks of treatment, spontaneous erections disappeared but adequate erection on mechanical stimulation remained.

The patient was carefully reexamined at the end of the 90-day period for evidence of toxic manifestations. There were no gastric intestinal complaints, no changes in the skin or the peripheral nervous system. Vibratory sense was intact and there was no deep muscle tenderness. Fundi were clear. Heart sounds were of good quality and of normal rate; blood pressure, 110/70. Liver and spleen were neither tender nor enlarged. There was no adenopathy. Blood count was as follows: R.B.C. 5,100,000 and hemoglobin 103%; white count 5,700 with 60% polynuclear, 39% leucocytes and 1% mononuclear. Fasting blood sugar was 90 mg. per 100 cc. The urine was clear; pH 7.6; Sp. G. 1.015 presenting no albumin, sugar or

formed elements. PSP over a period of two hours produced an 87% excretion of the dye. The total plasma cholesterol was 220 mg. and the cholesterol ester 111 mg. Urine creatine excretion on a meat-free diet for two successive 24-hour periods was as follows: preformed creatinine 1,428 mg. and 1,414 mg., creatine 744 mg. and 541 mg.

DISCUSSION

Testosterone propionate by inunction produced genital development definite enough to indicate physiological potency of this product in male hypogonadism although the ultimate result was not entirely satisfactory. Maximal stimulation was attained in one month without any further evidences of improvement over the subsequent two months of continued therapy. Possibly a diminution of the tissue sensitivity to a given dose of medication developed. An increase in the dose was out of the question since initial inunction of 3.5 gm. of the ointment twice daily (testosterone propionate 2 mg. per gm. of base) was too laborious to be practical, even in the hands of a hypogonad male anxious to improve his status. Foss (9) estimated that two to three times the amount used subcutaneously was required by inunction. A product of much greater concentration of the active principle (for example, 25 mg. or more of testosterone propionate per gram of inunction medium) is desirable and may be worthwhile.

Methyl testosterone appears to be a preparation, potent orally, in the stimulation of external genitalia and secondary sexual characters and as such is a drug of distinct promise in substitution therapy of male gonadal deficiency. No toxic manifestations have been noted to date although these were carefully sought. Two other cases show similar promise (10). Foss had previously reported success with methyl testosterone therapy. However, in view of the brevity of observations, no conclusions in this respect should be made until further prolonged and extensive experience in more cases is available. The promising findings to date should therefore be viewed only in the nature of a preliminary report.

CONCLUSION

Testosterone propionate applied percutaneously (14 mg. of the active principle in 7 gm. of medium per day over a 30-day period) to a hypogonad male was found sufficiently potent to stimulate a limited growth of the external genitalia and development of secondary sex characters. Methyl testosterone orally (40 mg. daily over a 90-day period) appeared to be a drug of considerable potency in the stimulation of growth of external genitalia, secondary sex characters and the libido.

REFERENCES

1. Hamilton, J. B.,: *Endocrinology* 21: 641. 1937.
2. Kenyon, A. T.: *Endocrinology* 23: 121. 1938.
3. Vest, S. H., Jr., and J. E. Howard: *J. Urol.* 40: 154. 1938.
4. Turner, H. H.: *Endocrinology* 24: 763. 1939.
5. Thompson, W. O., and N. J. Heckel: *J.A.M.A.* 113: 2127. 1939.
6. McCullagh, E. P.: *J.A.M.A.* 112: 1037. 1939.
7. Eidelsberg, J., and E. A. Ornstein: *Endocrinology* 26: 46. 1940.
8. Moore, C. R., J. K. Lamar and N. Beck: *J.A.M.A.* 111: 11–14. 1938.
9. Foss, G. L.: *Lancet* 2: 1284. 1938.
10. To be published.
11. Foss, G. L.: *British M. J.* 2: 11. 1939.

A STUDY OF UNTREATED "FRÖHLICH'S SYNDROME" WITHOUT BRAIN TUMOR[1]

ADIPOSOGENITAL DYSTROPHY

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BABINSKI (1) in 1900 described the case of a girl with obesity and failure to mature sexually. These symptoms were associated with an intracranial expanding lesion in the region of the sella turcica. Fröhlich (2) in 1901 described a boy with a similar clinical picture and diagnosed a tumor of the hypophysis. This syndrome of obesity and infantilism has come to be known as Fröhlich's syndrome or adiposogenital dystrophy.

The early experimental ablations of the hypophysis carried out by Crowe, Cushing and Homans (3), and by Aschner (4), suggested a hypopituitary origin to this syndrome. However, Camus and Roussy (5) and Bailey and Bremer (6) pointed out that these early operations were invariably accompanied by damage to the hypothalamus. These workers claimed this latter injury was the true cause of the syndrome. The conflict remained unsettled until the fundamental work of P. E. Smith (7). Smith was able to remove the hypophysis without injury to the hypothalamus and conversely, to produce a lesion in the hypothalamus without damage to the hypophysis (8). Marked obesity never resulted from hypophysectomy, whether complete or partial. Sexual maturation could be instantly arrested or prevented. Tremendous obesity resulted from injury to the hypothalamus.

The concept that hypopituitarism is responsible for obesity has nonetheless persisted in clinical usage. This has resulted in a more and more liberal interpretation of "Fröhlich's syndrome" to include a group of obese children without brain tumor but not as yet in puberty by age 11 or 12. On the basis of the postulated hypopituitarism, sex maturing agents such as pregnancy urine, pregnant mare's serum, and testosterone propionate have been administered. The favorable results of such therapy, however, have generally not been controlled by comparison with similar cases receiving no treatment. Gray (9) has recently presented two such cases maturing without treatment and Bruch (10) has studied a younger group of obese children with similar outcome. Ellis and Tallerman (11) have also observed the same result.

The present series of cases, presenting the diagnostic criteria currently implied by the term Fröhlich's syndrome, but without brain tumor, is reported here in order to re-emphasize the natural development that occurs when these children are left untreated except for weight reduction. Nine consecutive, unselected cases were followed in the Vanderbilt Clinic of the Presbyterian Hospital for from 2 to 4 years. No therapy was attempted except weight reduction. There were 8 boys and 1 girl. Two of the boys were 12 years old when first seen, the other children were

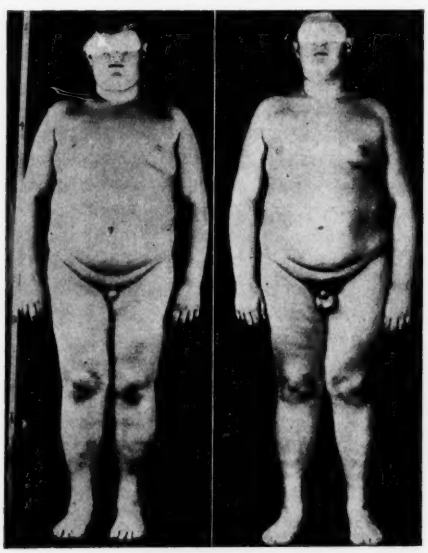

Fig. 1. A.F. P.H. Unit #549845. INFANTILE GENITAL DEVELOPMENT AND OBESITY AT 12 YEARS OF AGE AND SUBSEQUENT GENITAL MATURATION AT 15 YEARS OF AGE.

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[1] Aided by a grant for Teaching and Research in Neurology, Rockefeller Foundation.

between 13 and 15 (one of the boys was a negro). An additional boy of 15 without obesity but with infantile genitalia at the first visit has been included.

Seven of the 9 obese children were referred to the clinic by one or more doctors as Fröhlich's syndrome or "gland trouble." Two came because the parents were alarmed. The histories of the children were non-contributory aside from the chief complaint, except that the obesity was recent in origin in 4 of the children. Physical examination revealed weights 40 to 90% above expectancy (12), infantile genitalia without appearance of secondary sex characters, but no other abnormalities. Testes were descended in all the boys but were retractile in several instances.

All of the 10 children commenced and have completed the essential phases of normal puberty without incident during this study. Testes and penis have reached adult size and the one girl is now menstruating regularly. Signs of onset of sexual development were noted during the 13th to 14th year in 6 children, during the 15th year in 3, and after 16 in one. Some degree of weight loss was obtained at first in 7 of the 9 obese children but this weight was soon more than regained in all but 2. Normal height increase occurred in all.

Laboratory data revealed few abnormalities. Basal metabolic rates of −16 and −17% were found according to the Du Bois formula for surface area, in two of the cases. The other cases showed normal values. Fasting serum cholesterol values were normal, ranging between 168 and 225 mg.% in the 6 cases in which determinations were made, including one of the cases with a lowered metabolism. Bruch (13) has recently re-emphasized that the basal rate may be normal or low in obese children, depending on the unit of body measurement to which the actual caloric output is referred. Oral glucose tolerance tests were made in 6 instances. The curves were flatter than normal but the significance of this is dubious since the preceding type of diet was not controlled. In one instance the test was repeated after a week and was then normal. From x-rays of the epiphyses the bone age was described as normal in 8 cases. One patient showed an advance of 2½ years over the chronological age. X-rays were repeated in several instances after puberty had commenced. The previously normal bone age of 2 cases was described in the later x-rays as 2 and 3 years advanced. The epiphyses of the case considered to show premature development on the first x-rays, was found, 2 years later, to correspond to the chronological age. X-rays of the skull showed no abnormalities in any instance. Results of urinalyses, blood counts and blood Wassermann or Kline tests were normal.

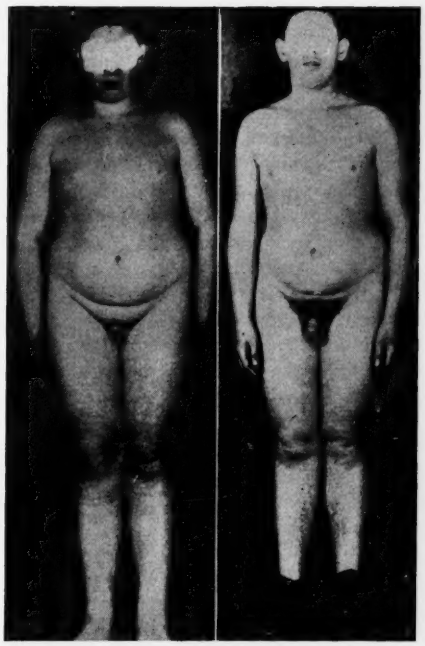

Fig. 3. *B.M.* P.H. Unit #511932. At 13 and 15½ years of age before and after onset of puberty.

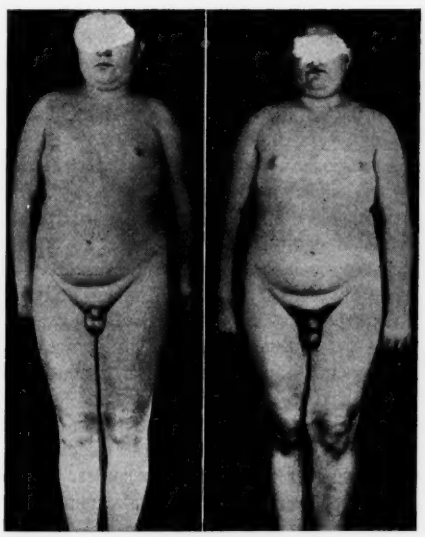

Fig. 2. *A.E.* P.H. Unit #503605. At 14½ and 17 years of age before and after onset of puberty.

DISCUSSION

A group of children satisfying current criteria for the diagnosis of Fröhlich's syndrome without brain tumor, have been followed for two to four years with

no treatment but diet. Spontaneous sexual maturity occurred in all. This development was fully as complete as that usually seen or reported after treatment with organotherapeutic agents. Puberty, moreover, commenced in 6 of the 10 cases within a short enough period of time after the first visit to be considered a therapeutic response to a hormonal preparation, had such an extract been administered. One child went into puberty only after 16 years of age.

These results suggest that this group of children should be observed for the occurrence of spontaneous puberty until about 16 years of age. No therapy would seem indicated except possibly weight reduction. Occasionally, psychological difficulties may make the induction of puberty desirable before this age, although such difficulties can usually be controlled before this procedure becomes necessary. The psychological aspect of the care of these children, however, is important and should not be neglected during the period prior to the onset of spontaneous puberty.

The obesity of these children has persisted in all but 2 instances in this series. Whether or not the presence of obesity in these subjects constitutes an abnormality has not been established. The experimental data at present do not support the hypothesis that obesity is caused by hypopituitarism. Clinically, Newburgh (14) has emphasized the non-endocrine aspects of obesity and energy balance. Moreover, the importance of the constitutional factors in obesity has been stressed (15), a point of interest here since these children exhibit the same morphological contours as a portion of the general population, who are usually considered to be normal. It may be found that varying degrees of glandular balance influence these differences in body build but since this concept has not yet led to a therapeutic regimen capable of changing constitutional patterns, the obesity in this group of patients is not at present an indication for any specific type of endocrine therapy.

Fig. 5. *H.S.* P.H. Unit #356835. Late onset of puberty in a boy without obesity, showing infantile development of genitalia at 15 and subsequent maturation at 18.

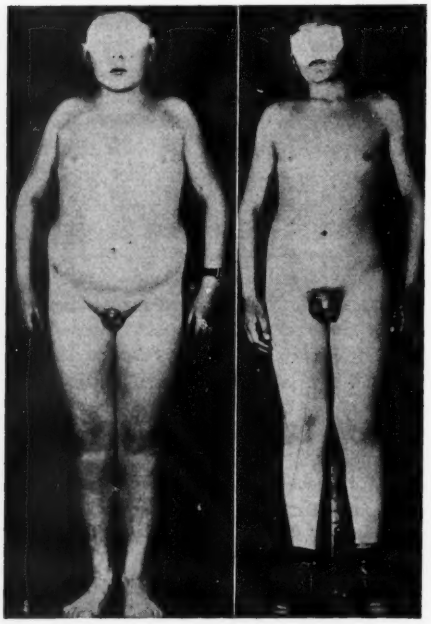

Fig. 4. S.K. P.H. Unit #51315. At 13 and 16 years of age, before and after onset of puberty.

The presence of a low basal metabolic rate in two instances, slightly flattened glucose curves and epiphyseal changes might possibly be interpreted as indicative of glandular abnormalities. However, these findings are inconstant. Furthermore, metabolic rates in this study were expressed in terms of body surface area, according to Du Bois's formula. As shown by Talbot (16), other standards of reference such as creatinine output, may change the value obtained. Thus the basal metabolism reading may give a misleading estimate of the actual degree of activity of the thyroid. Similarly, the glucose tolerance test is open to errors of interpretation unless conducted under rigidly controlled conditions taking into account preceding diet and absorption. Last, the estimation of bone age from the x-rays of the epiphyses is difficult as shown by the latitude of interpretation

between various authorities, and the causes of variation in epiphyseal age are not understood enough to warrant the conclusion that such changes, if real, may be referred solely to glandular function.

Thus, no constant evidence of glandular abnormality can be demonstrated in these children of the so-called Fröhlich type without brain tumor. Even though their clinical status should subsequently be shown to have an endocrine origin, one point may be stressed at present. These children mature sexually when left alone or simply dieted. This maturation is as adequate as that produced by any of the numerous therapeutic agents now used to induce puberty. Under the circumstances, it would appear unnecessary to use such agents except in the rare instance of severe psychological difficulty, in which the induction of premature puberty seems desirable. The foregoing discussion does not hold for those cases originally described by Babinski and Fröhlich where a brain tumor in the region of the hypophysis is present. Here the reason for disturbed hypothalamic and hypophyseal function is evident and the clinical picture may be reproduced by similar lesions induced experimentally.

SUMMARY

A study has been made of 9 children who fulfilled the current diagnostic criteria of Fröhlich's syndrome without brain tumor, and of an additional child not in puberty by the age of 15 years. These children all entered and went through a normal puberty without any treatment except moderate initial weight reduction. Laboratory data revealed no consistent demonstrable evidence of any endocrine disturbance. The conclusion has been drawn that these so-called Fröhlich children should not be given endocrine therapy unless they have not matured by 16 years of age.

REFERENCES

1. Babinski, J. J.: *Revue Neurol.* 8: 531. 1900.
2. Fröhlich, A.: Translation by H. Bruch., *Am. J. Dis. Child.* 58: 1282. 1939.
3. Crowe, S. J., H. Cushing and J. Homans: Bull. Johns Hopk. Hosp. 21: 127. 1910.
4. Aschner, B.: *Arch. f. d. ges. Physiol.* 146: 1. 1912.
5. Camus, J., and G. Roussy: *Rev. Neurol.* 38: 622. 1922.
6. Bailey, P., and F. Bremer: *Arch. Int. Med.* 28: 772. 1921.
7. Smith, P. E.: *J. A. M. A.* 88: 158. 1927.
8. Smith, P. E.: *Harvey Lecture* 25: 129. 1929.
9. Gray, H.: *J. A. M. A.* 110: 1430. 1938.
10. Bruch, H.: *Am. J. Dis. Child.* 58: 457. 1939.
11. Ellis, R. W. B., and K. H. Tallerman: *Lancet* 2: 615. 1934.
12. Gray, H., and J. S. Ayres: Growth in Private School Children. Behavior Research Fund Monograph. U. of Chicago Press, Chicago, 1931.
13. Bruch, H.: *Am. J. Dis. Child.* 58: 1008. 1939.
14. Newburgh, L. H., and M. W. Johnston: *J. Clin. Invest.* 8: 197. 1930.
15. Sheldon, Wm.: Varieties of Human Physique. Harper and Bros., New York, 1940.
16. Talbot, N. B., and J. Worcester: *J. Ped.* 16: 146. 1940.

ANDROGEN THERAPY IN PSYCHOSIS

EFFECT OF TESTOSTERONE PROPIONATE IN MALE INVOLUTIONAL PSYCHOTICS

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THE TREATMENT of female involutional psychoses with estrogenic substances naturally led to attempts at treatment of the male involutional states with corresponding products. Impetus was given to this study by the synthetic preparation of testosterone in 1935 by Ruzicka and also Butenandt, relating this substance structurally to the female sex hormones and also vitamin D. The historical development is concisely summarized in the studies of Kearns (1), Cary (2) and Eidelsburg (3).

The male climacteric has long been vaguely described. Werner (4) considers that the climacteric is due primarily to the decline of function of the sex glands. Donald (5) describes the male climacteric as an ill defined state of nervous instability. Improvement with testosterone therapy can be expected only in proportion to the degree of gonad responsibility, and the prognosis must be based on the purity of etiology and the extent of established organic changes.

In the severer forms when mental changes predominate, we are confronted with a problem not only in diagnosis but also in treatment. The transition into a psychosis is often so gradual that the onset is obscured. In April, 1939, at the Elgin State Hospital, there were 29 male patients diagnosed as having involutional psychoses: these constituted only 1% of the total male population. The mixed etiology was ever a problem and led to a careful critical reexamination of our material. Eleven of the 29 were deemed unsuitable because such factors as excessive alcoholism, mental deficiency, syphilis, arteriosclerosis and schizophrenia would confuse the final evaluation of therapy. Six others were considered questionable cases in that their diagnoses were a compromise. One patient was paroled as the study was begun. This selection of material resulted in a total of 11 male patients, a study of whose mental and physical reactions under therapy with testosterone proprionate, form the basis of this report.

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PROCEDURES

All of the patients had been in this hospital for varying periods of time (9 months to 6 years) and had not showed improvement. After the initial pretherapy data were completed, injections were begun with 10 mg. testosterone propionate twice weekly and continued for 3 months uninterruptedly. No effort was made to explain the purpose of the treatments, nor the various repeated procedures. In fact, there was little spontaneous patient interest. In order to evaluate more critically the effect of testosterone on the patients, not only the mental reaction, but also somatic changes which might be caused by the administration of the drug, were observed. Such data as blood pressures, weight, skin temperatures and mental reactions were checked periodically during the treatment regime. In several instances there were no significant variations, in others the observations were objective and easily reported, and in another group, the interpretations were subjective depending upon our own reactions and impressions. To minimize this possible source of error, we checked each other and obtained opinions from staff members, nurses and attendants. The group has now been observed for two months following cessation of therapy, and while some of the changes evidently produced have more or less persisted, others appear to have been transient deviations.

STUDY FACTORS AND OBSERVATIONS

Laboratory reports, careful inspection and measurements revealed no significant changes in prostatic smears, external genitalia, size and consistency of the testes, urinary constituents and complete blood counts.

Weight. A monthly check over a 5-month period was inconclusive. Four patients remained stationary, 5 lost from 4 to 16 lb., two gained from 3 to 8 lb.

Pubic hair (amount, type, distribution). A finer, straighter and less kinky type of hair appeared intermingled in almost negligible amount.

Genitourinary complaints. Nine expressed none; 2 suffered with nocturia, which was definitely improved.

Erections. Prior to therapy, 5 stated they obtained erections; 4 could not, and 2 were non-committal. All remained unchanged.

Skin temperatures. Using a Taylor dermatherm readings were taken from the forehead, back of right and left hand, and under right and left big toe; before injection and 1½ to 2 hours after. The interval was spent quietly in bed or sitting in day room. In 9 patients there was an average increase of 1.5° C. ranging from 0.3° in one to an average of 2.6° in another. One decreased 0.4° and one was too uncooperative for this test.

Prostate (size, consistency rectally). The gland felt enlarged but less firm in 3 patients. Examination after 2 months revealed that this enlargement persisted in 2 but had noticeably diminished in the third.

Blood pressures. Successive readings were taken

TABLE 1

	Age	Duration	Marital age 1st	Children No.	2nd	Hospitalization	Diagnoses	Symptoms
I.L.	55	5 yr.	26	5		1936 C.S.H. 1938 E.S.H.	Involl. melancholia Involl. psychosis (Paranoid depression)	Complaining, refused to eat with family, prepared own food, refused to bathe, lay in bed for hours, said he had cancer.
R.S.	54	9 yr.	22	5		1931 Resthaven (2) Sacred Heart 1931 E.S.H. 1935 E.S.H.	 Paranoid state Involl. psychosis (catat.)	Excited, impulsive, delusions of persecutions, becoming withdrawn, unkempt, adopted a rigid routine, thought food poisoned, refused medicine, had to be tube fed.
J.G.	58	9 yr.	21	6	42	1931 Pinel 1932 Mercyville 1933 E.S.H.	 Involl. melancholia	Somatic complaints, unkempt, worried, moaned, cried, wrung hands, thought food poisoned, said pipes would burst and children drown. Alcoholism.
T.H.	58	4 yr.	26	7		1937 E.S.H.	Involl. psy. depressed	Resistive and retarded, over-religious, spent money foolishly, thought his soul was lost, police after him, he was a sinner.
P.N.	53	2 yr.	27	5	32	1937 Fairview 1938 E.S.H.	 Involl. psychosis (Paranoid depression)	Worried, suspicious, depressed, self-accusatory, cried, attempted suicide, thought food poisoned, somatic delusions (said his bowels hadn't moved for 3 months).
A.G.	48	3 yr.	39	0		1936 E.S.H.	Involl. psychosis (Paranoid depression)	Nervous, retarded, fearful, refused to eat, self-accusatory (called self insane), spoke about suicide, hallucinated, alcoholism.
J.A.	65	10 yr.	28	2		1929 Sacred Heart 1936 E.S.H.	Anxiety depression Involl. psychosis (Paranoid)	Felt he was man of power, there was universal graft, irritable, saw G-men, guilt feelings pervert sex acts years ago, religious depression, pressure in head.
J.W.	64	2 yr. or 17?	25	5	54	1922–29. 3 Times in C.S.H. 1937 E.S.H. 1938 E.S.H.	Dem. praecox hebephrenic Anxiety neurosis Involl. psychosis depression	Nervousness, self-accusatory and deprecatory (calls self crazy, spoke of suicide), gets lost, insomnia, calls wife prostitute, noises in head.
M.G.	54	6 yr.	25	2		1933 Sanitarium 1934 K.S.H. 1936 E.S.H.	 Undiagnosed psychosis Involl. psychosis. Agitated depression	Anxious, depressed, lost nerve and taste for life, cried, self-deprecatory, attempted suicide twice with gas, repulsed by sexual contact. Echolalia.
W.F.	54	6 yr.	23	4		1938 E.S.H.	Involl. psychosis (Paranoid)	Irritable, railroaded under false pretenses, wants lawyer, waited for imaginary women in woods, planned underground flats for prostitutes, complained of saltpeter in coffee.
M.T.	46	9 mo. 4 yr.(?)	21	2		1935 Sanitarium 1939 E.S.H.	Neurasthenia Involl. psychosis Agitated anxiety form	Tired, slept poorly, crying spells, message from God, guilt feelings, impotency, feeling of external control, severe agitation, attempted suicide.

over 3 months under similar conditions. Ten patients had a fall in systolic pressure of 8 to 50 mm. and one increased 20 mm. Examination 2 months after therapy revealed that the blood pressure fall persisted in 3; the reading rose to the pre-therapy level in 5 and above that in 2.

Cystoscopy. A noticeable degree of prostatic encroachment developed in 4 patients. This involved the lateral lobes in 3 and the middle lobe in the fourth. There were no associated urinary complaints. Reexamination 2 months following cessation of therapy revealed that in one patient, lateral lobe encroachment was definitely less marked, while in the other 3 the findings persisted.

Dosage. Ten mg. was administered twice weekly intramuscularly for a total of 240 to 270 mg. One patient received 10 mg. every other day for 2 weeks and later 10 mg. daily for 2 weeks (a total of 400 mg.), with no beneficial effects observed.

Aspiration biopsy of testis. Under intravenous sodium amytal specimens of tissue were obtained before and at cessation of therapy. Examined microscopically after treatment they showed a definitely diminished spermatogenesis, as compared with pre-therapy sections. In none of the sections were spermatozoa observed following therapy. Considerable amounts of connective tissue were seen. Prior to treatment the germinal cells were somewhat indistinctly outlined and many of them appeared shrunken, while following therapy, the cell contours were much better defined.

Behavior and mental change (weekly interviews, impression of attendants, observation of relatives). Seven patients were definitely unchanged. Four became somewhat more alert, friendly and sociable, ate and slept better. When interviewed they still persisted in their old delusional ideas, and denied feeling any better or acting differently except for alleviation of head noises and cold extremities. Two (*P.N.* and *M.G.*) showed this change to a mild degree, while *J.W.* and *J.A.* were overtly more energetic and interested. These latter proclaimed their heads free of noises and pressure annoyingly present prior to therapy. *J.W.* described an improvement in the circulation of his extremities principally his left arm and leg, which previously felt continuously cool but now seemed warm and comfortable. Two months following therapy, one, *J.W.*, is at home. The remaining 3 are still in this hospital. Their transient improvement is no longer in evidence.

DISCUSSION

The literature on this subject revealed only four articles in which the mental aspect was recorded as a significant part of the study. Of these Barahal (6) concludes that this therapy produced no improvement. Five male patients were under treatment for 3 to 4 months receiving 10 mg. of testosterone propionate three times weekly. Haas (7) using 5 mg. doses 3 times weekly, describes good results in neurasthenia and involutional melancholia. Schmitz (8) states he has improved 36 of 42 patients in the involutional age and Weiss (9) considered recovered 12 male patients suffering from anxiety, depression and suicidal attempts. Titley (10) points out that the previous personality pattern is a definite factor besides the involutional changes. Most authors agree that such a complex as is described by involutional psychosis does exist. It is less frequent, not so well defined as the female involutional psychosis and manifests itself in several forms, paranoid, depressed or agitated. Usually about 55 years of age, such patients are found to be complaining, worried, suspicious, accusatory, with delusions of persecution, and of being poisoned. Suicidal attempts are frequent.

Among our own group, from all available data, 8 are described as revealing no noteworthy personality characteristics, one is said to have been very religiously inclined, another very quiet, reserved, having few friends, and a third stubborn. The records do reveal some interesting data. The average age of onset of the mental illness was 48.9 years. The average of their first marriage was 25.7 years, and they averaged 4.3 children. Eight of the 11 patients had been previously hospitalized from one to five times for some mental disorder.

What constitutes adequate dosage is still a debated question. In the male, we do not have the methods for gauging therapeutic dosage as have been developed for the female, i.e., the vaginal smear, vaginal acidity, and reaction of compound solution of iodine. Satisfactory results are described when using as little as 5 mg. 3 times weekly up to 25 mg.

TABLE 2

	P.N.	*J.A.*	*J.W.*	*M.G.*
Weight	Stationary	Stationary	Lost 6 lb.	Lost 4 lb.
Erections	Questionable	Present	Absent	Absent
G-U Complaints	None	None	Nocturia	None
Genitalia	Unchanged	Unchanged	Unchanged	Unchanged
Testes	Unchanged	Unchanged	Unchanged	Unchanged
Prostate	Unchanged	Somewhat enlarged	Unchanged	Unchanged
Cystoscopy	Unchanged	Middle lobe encroachment	Unchanged	Unchanged
Skin temperature	+1.6°	+0.9°	+1°	+2.6°
Dosage (total)	270 mg.	270 mg.	270 mg.	240 mg.
Blood pressure	Raised	Lowered	Lowered	Unaltered
Aspiration biopsy	Inconclusive	Delayed spermatogenesis	Delayed spermatogenesis	Delayed spermatogenesis

daily. Foss (11) states that 100 to 140 mg. are needed to restore function and then a maintenance dose of 40 mg. weekly. Kearns (1) considers that 20 mg. weekly or 28 mg. in ointment form is sufficient. Good sexual function without excessive libido results. Kenyon (12) reports that in normal adults 7 to 21 mg. of androgenic substance is excreted daily. Our dosage of 10 mg. twice weekly was selected as being therapeutically effective in view of the aforementioned opinions and clinical evidence.

The most generally accepted use is in the realm of substitution therapy. Lipross (13) describes an increased bladder muscle tonus, and both Kearns (1) and Kundstadter (14) warned of a possible secondary atrophy of the gonads. Rubinstein and Kurland (15) report the effect of testosterone on spermatogenesis. Following the administration of 5 mg. 3 times weekly the sperm count rose and after cessation of therapy returned to normal. Increasing the dosage to 25 mg. weekly resulted in lowering of the sperm count with return to normal after cessation of therapy. They found insignificant changes in genitals, pubic hair and libido. Kenyon (12) used 25 mg. daily in a eunuchoid and found that the few sperms present, disappeared to reappear when the drug was discontinued. These observations agree with our findings. Spermatogenic activity was evidently delayed even with 10 mg. twice weekly. Biological activity of testosterone propionate is definitely shown by the various changes described, particularly the increase in skin temperature and inhibition of spermatogenesis. The outstanding mental change, during the period under therapy, was transient, increased sociability and alertness, overtly detected in a few but definitely not sensed by the patients. The relief from head noises and pressure is probably associated with the alteration in circulation as evidenced by skin temperature changes. This along with subjective improvement in circulation opens another field of therapeutic possibilities. The personality disorganization of these patients was not appreciably altered by this drug, the subjective improvement being transient, such as has been repeatedly reported by other investigators.

SUMMARY

Eleven male patients diagnosed as involutional psychotics were treated with 10 mg. doses of testosterone propionate twice weekly for 3 months and observed for 2 months following cessation of therapy.

Blood counts, urinalyses, prostatic smears, external genitalia and testes, as well as erections, were seemingly unaffected.

Bladder muscle tone was apparently improved, alleviating symptoms of mild prostatic obstruction.

Blood pressure, pubic hair and weight changes were not significantly altered.

Skin temperatures showed a definite rise in most of the patients approximately two hours after injection.

The prostate, palpated rectally and observed cystoscopically, was slightly enlarged in a few but this appears to have been a transient alteration.

Sections of the testes obtained by aspiration biopsy revealed a decrease in spermatogenic activity following therapy.

While definite physiological changes have been observed proving the activity of the preparation, mental improvement was not sufficiently pronounced to warrant administering testosterone propionate as a routine treatment for the male involutional psychoses.

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We extend our thanks to Dr. Erich Liebert, Clinical Director, Elgin State Hospital, for his guidance and helpful suggestions.

REFERENCES

1. Kearns, W. M.: *J. A. M. A.* 112: 2255. 1939.
2. Cary, F. S.: *Illinois M. J.* 73: 486. 1938.
3. Eidelsberg, J.: *Med. Clin. N. America* 22: 1537. 1938.
4. Werner, A. A.: *J. A. M. A.* 112: 1441. 1939.
5. Donald, H. R.: *Clinical J.* 67: 323. 1938.
6. Barahal, H. S.: *Psychiat. Quart.* 12: 743. 1938.
7. Haas, A. L.: *Fortschritte der Therap.* 12: 676. 1937.
8. Schmitz, G.: *Deutsch. Med. Wchnschr.* 6: 230. 1937.
9. Weiss, O. L.: *Deutsch. Med. Wchnschr.* 65: 261. 1939.
10. Titley, W. B.: *Arch. Neur. & Psych.* 36: 19. 1936.
11. Foss, G. L.: *Lancet* 1: 1307. 1937.
12. Kenyon, A. T.: *Endocrinology* 23: 121. 1938.
13. Lipross, O.: *Münchn Med. Wchnschr.* 85: 1668. 1938.
14. Kundstadter, R. H.: *Endocrinology* 23: 661. 1938.
15. Rubinstein, H. S., and A. A. Kurland: *Southern M. J.* 32: 499. 1939.

PREGNANCY AND SEX HORMONE EXCRETION

DAY AND NIGHT EXCRETION OF PREGNANDIOL GLUCURONIDATE AND NEUTRAL 17-KETOSTEROIDS IN PREGNANCY

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IN ADDITION TO major variations over fairly long periods, the urinary excretion of pregnandiol glucuronidate during pregnancy shows minor daily fluctuations (1–4). On preliminary examination the variations between one 12-hour period and the next appeared to be no greater than they were from day to day (4). We have therefore investigated the feasibility of substituting 12- for 24-hour determinations in the study of this compound, because of certain advantages which may be gained by such substitution. Thus, not only is the collection of 24-hour specimens an inconvenience to many subjects and therefore often inaccurately made, but, since the compound is unstable in urine, losses are apt to be more serious during 24-hour than during 12-hour periods of accumulation. Again, it may occasionally be desirable to obtain results more promptly than is possible if an entire day is consumed merely in securing the specimen to be examined.

In the present study attention has been given to the relation of the short-term output of pregnandiol glucuronidate to the longer-term trends and levels of output, as also to the time of day during which the urine is collected, and to the volume output of the urine. The last 2 points were of particular interest because Lansbury and Hughes (5) have recently reported that in non-pregnant women the estrin content per liter of urine is essentially similar in both day and night specimens, although the day volume is usually twice that of the night volume. Finally, opportunity was taken to examine the simultaneous excretion of neutral 17-ketosteroids in a number of the specimens collected, in order to determine in how far any short-term fluctuations in the output of these substances resembled those of pregnandiol.

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METHODS

The characteristics of the daily excretion of pregnandiol glucuronidate were examined in 13 pregnant women, among whom the simultaneous output of 17-ketosteroids was studied in 3. The subjects were selected in such a manner as to provide examples of both normal and abnormal gestation at various stages of maturity. Eight of the patients were confined to bed in hospital. In 6 of these, one or more days' excretions were collected at intervals of 6 hours. In the remaining 7 patients, the collections consisted of 12-hour samples, accumulated consecutively for periods ranging from 1 to 7 days. These represented the day and night excretions, since they were started at 8 A.M. and 8 P.M. respectively. In order to ensure as much accuracy as possible in the collection of complete specimens, the hospitalized patients were housed in a carefully supervised study ward, and the selection of ambulant patients was restricted to the wives of professional colleagues whose interest had been enlisted.

During the collection periods the specimens were placed in an ice-box immediately after being voided, and the accumulations were kept chilled until their work-up, which was, with one exception (*case 11*), not delayed longer than 15 hours. Cold storage of the urine was found to be necessary for ensuring accurate determinations of pregnandiol glucuronidate. Control experiments showed that, in spite of the use of preservatives, this compound may undergo a more rapid hydrolysis in unchilled urine than has previously been suspected (1). Thus, even the considerable amounts of it which are present in urine of late pregnancy may completely disappear within 24 hours if the urine is kept at 25°; on the other hand, losses are hardly appreciable even after 2 weeks, if the urine is preserved at 0–5°[1].

The methods of isolating pregnandiol glucuronidate from the urines, and of checking its purity, were those previously reported (4), being essentially the ones devised

[1] An alternative method of preservation may be employed by extracting the compound from the fresh urine with butanol; in the latter solvent no significant losses of glucuronidate could be detected after 3 weeks of standing at room temperature.

by Venning and Browne (1, 6, 7). In conformity with previous reports the results have been recorded in terms of free pregnandiol.

For the determination of the neutral 17-ketosteroids the color reaction of Zimmermann (8) was employed, with the modifications recommended by Callow, Callow and Emmens (9). The procedures for the hydrolysis and extraction of urine and the preparation of extracts were essentially those developed by the latter authors (10); these methods yielded quantitative recovery of 17-ketosteroids added to urine. The Evelyn photoelectric photometer was used for measuring the extinction of the color products in 2 spectral regions with the use of filters transmitting maximally at 420 and 520 mμ. In each determination a correction was made for the color developed by the urinary extract in the presence of all the reagents except the dinitrobenzene. Extinction at 520 mμ was compared with that of the pigment developed by varying amounts of androsterone.

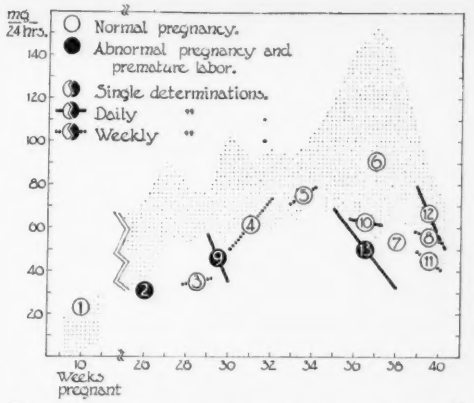

Fig. 1. Pregnandiol excretion in 13 pregnant women. Abscissa represents menstrual age of pregnancy in weeks. Ordinate shows output of pregnandiol, determined from 12-hr. specimens, and calculated in mg./24 hours. Data are plotted against a background (stippled area) showing ranges of normal excretion as determined in a separate group of 6 women, studied individually throughout gestation. See text for clinical data appertaining to patients whose records are here illustrated; the numerals in the circles refer to the individual case numbers.

RESULTS AND DISCUSSION

Pregnandiol excretion. Figure 1 illustrates the average level of the patients' daily excretions of pregnandiol; the latter are plotted against a background representing the ranges of daily excretion previously obtained in a group of 6 healthy women who had been studied individually throughout gestation (4). Five of the patients of the present study had normal pregnancies (*cases* 1, 3, 5, 8 and 10), of whom 4 showed normal levels of excretion. Of the remaining 8 patients 3 suffered from complications which have previously been shown (11, 12) to depress the excretion of pregnandiol, i.e., advanced chronic hypertensive disease (*cases* 2 and 9), and pre-eclampsia (*case* 13); in 2 of these patients (*cases* 9 and 13) pregnancy terminated in spontaneous premature labor. Finally, 5 patients (*cases* 4, 6, 7, 11 and 12) exhibited no abnormality of gestation which is known to affect the excretion of pregnandiol, and their daily excretions were, in fact, within the normal range (fig. 1); 4 of them, however, suffered from circulatory or excretory disorders which

Table 1. Day and night excretion of pregnandiol at various periods of pregnancy

Case No.	Maternal condition	Weeks pregnant	Urine volume			Pregnandiol		
			Day	Night	Duv/Nuv	Day	Night	Dp/Np
			cc.	cc.		mg.	mg.	
1	Normal (A)[1]	10	980	715	1.37	11.5	11.2	1.03
2	Nephrosclerosis (B)[1]	26	875	610	1.43	13.6	16.6	0.82
3	Normal (A)	28	1320	350	3.77	17.6	16.6	1.06
		29	1000	370	2.70	13.0	21.6	0.60
4	Tuberculosis (B)	30	1720	795	2.16	21.7	28.1	0.77
		32	2020	2120	0.95	39.0	35.2	1.11
5	Normal (A)	33	765	1330	0.58	27.1	44.7	0.61
		34	600	1530	0.39	32.8	46.0	0.71
6	Hypoproteinemia (B)	37	530	745	0.71	44.7	45.7	0.98
7	Endocarditis (B)	37	380	235	1.62	33.8	22.4	1.51
8	Normal (A)	39	430	470	0.91	26.5	31.4	0.84
		40	540	575	0.94	25.0	28.7	0.87
	Average:				1.46			0.91

[1] (A)=ambulant; (B)=bedfast.

TABLE 2. DAY AND NIGHT EXCRETION OF PREGNANDIOL AND 17-KETOSTEROIDS DURING 5 TO 7 CONSECUTIVE DAYS

Case No.	Maternal condition	Weeks pregnant	Urine volume			Pregnandiol			17-ketosteroids		
			Day	Night	Duv/Nuv	Day	Night	Dp/Np	Day	Night	Dk/Nk
			cc.	cc.		mg.	mg.		mg.	mg.	
9	Chronic hypertension (B)[1]	29	640	760	0.84	29.2	27.5	1.06	5.6	4.9	1.14
			715	810	0.88	28.0	26.0	1.08	4.5	4.4	1.02
			650	890	0.73	21.2	16.9	1.25	3.9	3.6	1.08
			600	930	0.65	17.5	15.1	1.16	2.7	4.0	0.68
			980	765	1.28	19.6	15.2	1.29	4.3	3.4	1.26
			380[2]	930	0.41	10.0	14.2	0.70	2.9	2.9	1.00
					0.80			1.09			1.03
10	Normal? (A)[1]	36	260	190	1.37	36.4	38.0	0.96			
			225	235	0.96	26.3	26.3	1.00			
			420	530	0.80	46.6	41.3	1.13			
			305[2]	615	0.50	17.0	32.8	0.52			
			790	715	1.10	30.3	33.2	0.91			
			450	400	1.13	29.5	30.5	0.97			
			850	620	1.37	28.6	23.1	1.24			
					1.03			0.96			
11	Hypoproteinemia (B)	39	1080	390	2.77						
			690	540	1.28						
			675	130[2]	5.20	118.1	138.9	0.85	60.7	43.8	1.39
			580	710	0.82						
			740	575	1.29						
			440	835	0.53						
					1.98						
12	Chorea (B)	39	450	320	1.41	39.4	39.8	0.99	8.9	6.2	1.44
			340	300	1.13	30.8	27.5	1.12	5.1	5.0	1.02
			820	650	1.26	24.6	18.4	1.34	7.6	5.4	1.41
			520	310	1.68	22.0	26.2	0.84	6.5	5.5	1.18
			685	460	1.49	35.2	20.3	1.73	7.6	5.1	1.49
					1.40			1.20			1.31

[1] (B) = bedfast; (A) = ambulant.
[2] Collections incomplete.

might be expected to affect the ratios of the day: night output of urine and of urinary excretion products, i.e.—hypoproteinemic edema (*cases* 6 and 11) and endocarditis (*cases* 7 and 12). It will be noted that in 4 of the patients in whom repeated records of excretion were obtained, the output of pregnandiol was declining during the period studied (*cases* 8, 9, 12, 13); all of these patients began labor within a few days of the completion of their urine examinations; during this study, therefore, they exhibited the drop in excretion which was found by previous investigation to be characteristic of the pre-labor period (4).

The details of the day and night excretion of pregnandiol in these cases may be seen in tables 1 and 2. Irrespective of the maturity or character of gestation, the day and night output of pregnandiol was usually about equal, the mean ratio of day: night excretion (Dp: Np) being 0.99 and the standard deviation ±0.24. The extremes of this ratio exceeded 1.5 only twice, and fell to 0.6 only once in 36 examinations. It should be noted, however, that while these findings appear to be true even for periods wherein the general day-to-day curve of output is falling (*cases* 9, 10 and 12), they may not always be valid for the days immediately preceding labor. Thus, in one patient, previously reported (4), who was studied at 6-hour intervals ending on the day of labor, the output in the last 4 consecutive periods was 28, 23, 12 and 9 mg.

Excretion of 17-ketosteroids. In the comparatively few instances wherein the day and night excretion of the 17 ketosteroids was determined (*cases* 9, 11 and 12 of table 2), the same general characteristics were observed as were found for pregnandiol.[2] In one patient (*case* 11), however, the mean of one week's day: night

[2] Callow et al. (10) have found that the 17-ketosteroids are "present in higher concentration in the morning urine than in that passed during the rest of the day." Without a more definite reference to time relationships than this, it is not possible to compare their findings with our own, nor to infer that they are inconsistent with an approximately equal distribution of the ketosteroids between the 12-hour day and 12-hour night urine.

TABLE 3. RELATION OF DAY AND NIGHT VOLUMES OF URINE TO DAY AND NIGHT EXCRETIONS OF PREGNANDIOL

No. of ratios	Urine volume, day:night ratio		Pregnandiol, day:night ratio
16	0.10–0.99,	m= 0.73	0.92
15	1.00–1.99,	m= 1.35	1.10
5	2.00 and over,	m= 3.32	0.83
36		m= 1.35	0.99
		S.D.=±0.95	±0.24
		$S.E._m$=±0.16	±0.04

m=Mean. S.D.=Standard deviation. $S.E._m$=Standard error of mean.
$S.E.(m_{UV}-m_P)$=0.16.

ratio for 17-ketosteroids differed appreciably from that of the ratio for pregnandiol excretion over the same period. Since no studies of 17-ketosteroid excretion throughout gestation have so far been recorded, further work along these lines is desirable, and is now under way.

Relation of day and night excretion of pregnandiol and 17-ketosteroids to the volume output of urine. Although the 4 to 7-fold increase in daily output of pregnandiol which takes place between the 3rd and 10th month of gestation makes it obvious that there can be no basic relation between urine volume and the amounts of this compound's excretion, the findings of Lansbury and Hughes (5) relative to estrogen excretion suggested that diurnal fluctuations of urinary volume may induce temporary fluctuations in the output of either pregnandiol or the 17-ketosteroids, or both. That such is not the case for pregnandiol, however, was suggested by our previous studies (4). and has been verified for both groups of steroids by the data illustrated in tables 1 and 2. These show wide fluctuations in the ratios of the day and night volumes of urine, with no corresponding variations of pregnandiol or ketosteroid output. In *case 10*, moreover, a temporary oliguria was induced by subjecting the patient to a dehydration regime prior to beginning the study of her excretions; as will be noted, her rehydration and the return of her 24-hour urine volume to normal during a period of 3 days brought about no accompanying rise in output, or 'flushing-out,' of either pregnandiol or ketosteroid. The lack of correlation between urine volume and pregnandiol excretion indicated by these data has been illustrated in table 3.

Relation of day and night to 24-hour excretion of pregnandiol and 17-ketosteroids. In table 4 data are analyzed from 3 patients in whom determinations of pregnandiol and 17-ketosteroids were made upon successive 12-hour samples of urine for periods of from 5 to 7 days. For each of these compounds the mean of the ratios of one day's excretion to the next day's has been compared with the mean of the ratios of each daytime excretion to the succeeding nighttime output, and the mean of the ratios of each nighttime excretion to the succeeding daytime output. From figure 1 and table 2 it will be noted that in all of these patients the output of the steroids was declining during the periods of observation, a fact which is illustrated by the mean values of the day-to-day ratios, i.e., 1.15 for pregnandiol and 1.11 for the 17-ketosteroids. These ratios rarely varied by more than 30% from day to day. The calculations listed in table 4, moreover, demonstrate that the declining trends were as satisfactorily reflected in the 12- as in the 24-hour excretions, and that there was no constant preponderance of the diurnal over the nocturnal output, or vice versa. The cases analyzed, however, include only one example (*case 9*) wherein the general range of steroidal excretions were abnormal; that the findings are nevertheless probably true for other instances of abnormal excretion is suggested by the data of *case 13*. This patient, a case of severe pre-eclampsia, was studied daily during the period of her most acute symptoms for a total of 19 consecutive examinations (12); the determinations showed a gradually declining level of daily output, the mean of the day-to-day ratios being 1.09, while the standard deviation was 0.32. Although 12-hour specimens were not examined in this case the relative smoothness of the curve of daily output over an extended period resembles the

TABLE 4. VARIATION IN EXCRETION OF PREGNANDIOL AND 17-KETOSTEROIDS DURING SHORT CONSECUTIVE INTERVALS

Case No.	No. of days (n)	Pregnandiol			17-ketosteroids		
		$\frac{1}{n-1}\sum_{\nu=1}^{n-1}\frac{D_\nu+N_\nu}{D_{\nu+1}+N_{\nu+1}}$	$\frac{1}{n}\sum_{\nu=1}^{n}\frac{D_\nu}{N_\nu}$	$\frac{1}{n-1}\sum_{\nu=1}^{n-1}\frac{N_\nu}{D_{\nu+1}}$	$\frac{1}{n-1}\sum_{\nu=1}^{n-1}\frac{D_\nu+N_\nu}{D_{\nu+1}+N_{\nu+1}}$	$\frac{1}{n}\sum_{\nu=1}^{n}\frac{D_\nu}{N_\nu}$	$\frac{1}{n-1}\sum_{\nu=1}^{n-1}\frac{N_\nu}{D_{\nu+1}}$
9	6	1.20	1.09	1.09	1.14	1.03	1.12
10	7	1.13	0.96	1.28	—	—	—
12	5	1.12	1.20	1.00	1.07	1.31	0.86
	18	1.15	1.07	1.14	1.11	1.15	1.01
		S.D.±0.30	0.25	0.43	0.21	0.15	0.21

S.D.=Standard deviation.
For explanation of symbols see text.

declining curves observed in normal cases, and suggests that the consecutive 12-hour outputs are hardly likely to have been more variable than they were found to be in the latter cases.

Since there is no theoretical advantage, therefore, in examining 24- instead of 12-hour specimens of urine, the choice of either type of sample may be left to such practical considerations as the convenience of the patient or examiner, the accuracy with which the urine will be collected, and the care with which it will be kept chilled prior to its work-up in the laboratory.

SUMMARY

Examination of the urinary output of pregnandiol glucuronidate in 13 pregnant women has shown that, despite fluctuations which occur over fairly long periods, the amounts excreted in successive 12- or 24-hour periods rarely differ by more than 30%. There is no constant preponderance of the 12-hour diurnal over the 12-hour nocturnal output, or vice versa. The mean of 36 ratios of the diurnal:nocturnal excretion was 0.99 ± 0.24. The amounts excreted are not related to the volume output of urine, nor are they influenced by disorders of maternal water metabolism or circulation. These characteristics, moreover, are found not only among pregnant women in whom the general levels of pregnandiol excretion are normal, but also among those in whom they are abnormal. Similar findings have been obtained for the excretion of neutral 17-ketosteroids, which were simultaneously studied in 3 patients. The use of 12-hour samples of urine for investigating pregnandiol and 17-ketosteroid excretion is therefore justifiable, since recoveries obtained from such samples will usually provide as accurate a reflection of current levels and trends of excretion as will those of 24-hour specimens.

REFERENCES

1. Venning, E. H.: *J. Biol. Chem.* 126: 595. 1938.
2. Wilson, R. B., and L. M. Randall: *Proc. Staff Meetings Mayo Clinic* 13: 813. 1938.
3. Smith, G. V. S., and O. W. Smith: *Am. J. Obst. & Gynec.* 39: 405. 1940.
4. Bachman, C., D. Leekley and H. Hirschmann: *Am. J. Med. Sc.* 200: 143. 1940; *J. Clin. Investigation* 19: 801. 1940.
5. Lansbury, J., and J. Hughes: *Endocrinology* 26: 609. 1940.
6. Venning, E. H.: *J. Biol. Chem.* 19: 473. 1937.
7. Venning, E. H., and J. S. L. Browne: *Proc. Soc. Exper. Biol. & Med.* 34: 792. 1936.
8. Zimmermann, W.: *Ztcshr. f. physiol. Chem.* 233: 257. 1935; 245: 47. 1936.
9. Callow, N. H., R. K. Callow and C. W. Emmens: *Biochem. J.* 32: 1312. 1938.
10. Callow, N. H., R. K. Callow, C. W. Emmens and S. W. Stroud: *J. Endocrinol.* 1: 76. 1939.
11. Weil, P.: *Science* 87: 72. 1938.
12. Bachman, C., D. Leekley and H. Hirschmann: *Journal of Clinical Endocrinology* (in press).

CORPUS LUTEUM STUDIES III. PROGESTERONE THERAPY IN CHRONIC CYSTIC MASTITIS

MAMMARY DYSPLASIA

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THE CONCLUSION that the various forms of mammary dysplasia result from ovarian dysfunction has led to attempts to control the disease with endocrine therapy. The largest number of cases has been treated with estrogen, presupposing an ovarian deficiency. The results of estrogen therapy in cases of chronic cystic mastitis have been reported (1). The male sex hormone (testosterone propionate) has been advocated by those who believe that its use counteracts estrin, and that hyperestrinism (an ovarian hyperfunction) may be a factor in chronic cystic mastitis. Since the cases of mammary dysplasia reported in a previous paper (2) show a deficiency in corpus luteum secretion, as measured by pregnandiol studies on the urine, progesterone therapy seemed logical.

Progesterone therefore was given to 27 patients with chronic cystic mastitis including the sub-varieties of mastodynia, adenosis and cystic disease. Of this group of 27 patients, 11 had urinary pregnandiol determinations (2). The results following progesterone injections are reported in the present paper and the course of symptoms in the patients so treated compared with similar cases following estrogen, surgery or no treatment.

Mastodynia. Thirteen cases of mastodynia were treated with progesterone. The hormone was administered in oil, intramuscularly in doses of 5 mg. twice weekly for the last two weeks of one or two consecutive menstrual cycles. The total dose varied from 20 to 40 mg. The ages of the patients treated ranged from 26 to 47 years. The majority of these were childless women and 8 were married but sterile (table 1A). The symptoms of pain, nodularity and tenderness in one or both breasts had been present for a year or more in most cases prior to treatment. Six of the 13 patients were treated for recurrence following previous estrogen therapy.

Two of the 13 patients with mastodynia had pregnandiol determinations on the urine prior to progesterone therapy. These were low, 13.2 mg. and 14.5 mg. per cycle (normal 26.2 to 58.5 per cycle, Bucher and Geschickter). One of the patients (*Hun.* table 1A) successfully treated had pregnandiol determinations on the urine following progesterone therapy. The determination was normal, 37.0 mg. per cycle.

All of the patients showed improvement with the exception of one who failed to finish the course of treatment and reported herself worse 7 months later. Those successfully treated remained well from one to two years after which time three cases had recurrent symptoms. The improvement following 30 mg. of progesterone therapy in one case lasted only two months, but responded to 5 mg. once weekly for two months.

Adenosis. Seven patients with adenosis were treated with progesterone therapy. The hormone was administered in the same fashion as in the cases with mastodynia. The total doses range from 20 to 60 mg. The ages of the patients were from 27 to 45 years. All the patients were married but only two had children (table 1B). Five of the 7 cases had symptoms of pain and nodularity for one to four years. Two were treated for recurrence following estrogen therapy. Four of the patients remained well from one to one and a half years and were well when last heard from. Another had recurrent symptoms after being well for 4 years.

One of these cases is of special interest (*Mal.* table 1B). She was aged 31, married for 5 years, and was sterile. She had bilateral painful breasts which were shotty, and had recurrent sick headaches for four years. She was treated in December, 1937 with progesterone therapy, 5 mg. every other day for a month, a total of 60 mg. She became pregnant the following month and was delivered of a normal child in August, 1938. She had a miscarriage in July 1940.

Two of the patients with adenosis had pregnandiol determinations before progesterone therapy. Both of these (*Shep.* and *Flu.*, table 1B) were low, 12.8 and 10.9 mg. One patient (*Sim.*, table 1B) had a normal pregnandiol excretion, 36.7 mg., following therapy.

Cystic disease. Among the 7 patients with cystic disease treated with progesterone therapy there were only 3 in which the treatment could be considered as influencing the disease. In all 3 cases there was a small solitary cyst (*McInt., Prin., Kohl.*, table 1C) at the time of treatment. In these 3 cases the cysts were reduced to a small indefinite fibrous area. One patient (*Zin.*) had recurrent multiple cysts in spite of a course

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TABLE 1. A. PROGESTERONE THERAPY IN MASTODYNIA

Patient	Age	Menses	Findings	Therapy[1]	Result
Lev.[2] Married, no pregnancies	28	Regular, 25-day cycle	Painful, lumpy breasts. Nodule in left breast, 1 yr. duration	Progesterone 40 mg. August, 1938	Recurrent symptoms continued sterility June, 1940
Hun. Married, no children	30	Always irregular	Painful lumps in both breasts, granular areas; 5 mo. duration	Progesterone 40 mg. March, 1938. Progesterone 20 mg. April, 1939	Lumpiness disappeared Recurrent soreness Well in March, 1940
Fau. Single	37	Regular, 28-day cycles	Painful indurated lumps in both breasts (one excised for diagnosis Feb. 1938); recurrent symptoms, April, 1938; 15 mo. duration	Progesterone 30 mg. April, 1938	Well in June, 1939
McCul.[2] Married, no children (lost 1 pregnancy)	33	Irregular, usual cycle is 26 days	Soreness in both breasts. Dense granular area; 4 yr. duration	Estrogen therapy Nov. & Dec. 1936. Progesterone 20 mg. Nov. 1939	Well for 3 yr. after estrogen therapy. Recurrence 1939 Well June, 1940
Shev. Married, one abortion, sterile for 2 yr.	32	Regular, 28-day cycles	Tender nodules at periphery of both breasts; 2 yr. duration	Progesterone 40 mg. June, 1938	Well June, 1940
Shap. Married, 2 children	38	Regular	Severely painful breasts with bilateral dense areas (biopsied elsewhere); 8 yr. duration	Estrogen therapy Dec. 1939. Progesterone 60 mg. April & June 1940	No improvement Improved
Hof. Married, 1 child	28	Regular, 26-day cycles	Tender nodularity about periphery of both breasts; 2 yr. duration	Progesterone 30 mg. July & Aug. 1938	Well in Oct. 1939
Bur. Married, sterile	29	Hysterectomy	Dense tender area in left breast; 3 mo. duration	Estrogen therapy followed by prolactin April, 1937. Progesterone 20 mg. Dec. 1937	Recurrence Dec. 1937 Well Jan. 1939
Amo. Married, sterile	33	Hysterectomy	Bilateral dense tender nodules; 2 yr. duration	Estrogen therapy May & June, 1938. Progesterone 30 mg. Dec. 1939	Recurrence Dec. 1939 Well April, 1940
Smi. Married, 2 children	42	Hysterectomy	Unilateral dense nodules; 2 yr. duration	Progesterone 40 mg. Nov. & Dec. 1939	Well June, 1940
McEl. Married, 1 child. No subsequent pregnancy for 12 yr.	30	Regular, 26 or 27-day cycles	Tender dense area in left breast; 1 yr. duration	Estrogen therapy April, 1939. Progesterone 25 mg. Dec. 1939	Improvement Recurrence Well in June, 1940
Duf.[3] Married twice, no children	26	Fairly regular, pain	Bilateral dense areas and tenderness; 1 yr. duration	Progesterone 10 mg. Nov. 1939	No improvement June, 1940
Ken.[3] Married, no pregnancies	47	Menses regular, 28-day cycles	Pain and small lump in left breast; 6 mo. duration	Estrogen therapy Dec. 1938. Progesterone 15 mg. Nov. & Dec. 1938, Jan. 1939	Recurrent April ,1940

[1] Progesterone administered in 5 mg. doses intramuscularly twice weekly for last two weeks of cycle for one or more consecutive cycles.
[2] Pregnandiol studies carried out on urine before progesterone therapy.
[3] Patient did not return to complete course of injections.

of progesterone therapy totaling 40 mg. In the remaining 3 patients the cyst had been previously treated by aspiration or excision and the treatment was given to prevent recurrence. These three patients have remained well one or two years. Four patients with cystic disease had assays performed on the urine for estrogen or pregnandiol. The pregnandiol values were normal before and low following the development of the cyst (2).

DISCUSSION

Endocrine therapy in mammary dysplasia has definite limitations. Accurate clinical recognition of the disease and its sub-varieties is essential. If the various forms including mastodynia, adenosis and cystic disease cannot be distinguished one from the other and doubt concerning the presence of cancer exists, exploration should be performed. Endocrine therapy may then be used when the condition is bilateral or

B. Progesterone therapy in adenosis

Patient	Age	Menses	Findings	Therapy[1]	Result
Hes. Married, 2 children	28	Irregular, profuse	Painful, shotty, bilateral; 2 mo. duration	Progesterone 30 mg. June & July, 1936	Recurrent soreness June, 1940
Pay. Married, childless	33	Functional bleeding	Painful, shotty, bilateral; 14 mo. duration; discharge right nipple; biopsy elsewhere; endometrial hyperplasia	Progesterone 40 mg. Sept. 1939	Well June, 1940
Shep.[2] Married, 3 children	45	Irregular	Pain, multiple nodules, small cysts; bilateral biopsy; 4 yr. duration	Progesterone 50 mg. Dec. 1938 & Jan. 1939. Former estrogen prolactin therapy 1936 & 1937	Recurrence 1938 Well June, 1940
Sim.[2] Married, no children	32	26-day cycles	Painful, lumpy, shotty, bilateral; biopsy elsewhere; 4 yr. duration	Estrogen therapy 1935 & 1937. Progesterone 20 mg. Aug. & Sept. 1938	Recurrence 1937 Well April, 1940
Tom. Married, sterile	32	Scant, 25-day cycles	Bilateral, tender, shotty masses; 6 mo. duration	Progesterone 40 mg. May, 1940	Well June, 1940
Flu.[2] Married, no children	27	Irregular	Painful, shotty; biopsy elsewhere; 2 yr. duration	Progesterone 30 mg. May, 1939	
Mal. Married, sterile	31	24-day cycle	Shotty, tender nodules, bilateral; 4 yr. duration	Progesterone 60 mg. Dec. 1937	Improvement, first child August, 1938, well since

C. Progesterone therapy in cystic disease

Patient	Age	Menses	Findings	Therapy[1]	Result
McInt. Married, 4 children	36	Profuse	Small cyst in right breast; 2 mo. duration	Progesterone 30 mg. Nov. & Dec. 1936	Only fibrous area remains. No symptoms April, 1940
Pin. Married, sterile	31	Dysmenorrhea, 28-day cycles	Cyst in left preast; previous cyst in right breast excised; 11 mo. duration	Progesterone 40 mg. June, 1939	Small flat disc of thickening only remains, Jan. 1940
Kohl. Married, 1 child	33	Regular	Small cyst left breast surrounded by dense areas; 4 yr. duration	Estrogen therapy Oct. 1936. Progesterone 30 mg. Feb. 1938, May, 1940	Only small fibrous area remains June, 1940
Zin.[2] Married, 1 child	42	Irregular, 24-day cycles	Multiple cysts, bilateral; 6 mo. duration	Progesterone 40 mg. Jan. 1939	Temporary improvement. Recurrent in 8 mo. Progressively worse Multiple aspirations 1940
Prin.[2] Married, 4 children	43	Regular, 28-day	Large solitary cyst in right breast; 1 mo. duration	Aspiration Dec. 1938. Progesterone 40 mg. Jan. 1939[3]	Well April, 1940
Lut.[2] Married, 2 children	41	Regular, 27-day cycles	Solitary cyst in right breast; 1 mo. duration	Excision Aug. 1938.[3] Progesterone 60 mg. Sept. 1938[3]	Well June, 1940
Gos.[2] Married, 2 children	32	Regular, 28-day cycles	Small multiple cysts in breast; 1 wk. duration	Excision July, 1939. Progesterone 30 mg. Aug. 1939[3]	Well June, 1940

[1] Progesterone administered in 5 mg. doses intramuscularly twice weekly for last 2 weeks of cycle for one or more consecutive cycles.
[2] Pregnandiol studies carried out on urine before progesterone therapy.
[3] Progesterone therapy given after aspiration or excision to prevent recurrence.

recurrent after its nature has been histologically verified. Among 77 patients referred for endocrine therapy, 4 doubtful patients were explored and found to have cancer, although the referring physician was convinced on clinical examination that the lesion was benign. In view of this experience it seems unwise for the practitioner to administer this form of treatment without consultation to confirm his diagnosis.

Endocrine therapy cannot be considered as specific in the treatment of mammary dysplasia until the exact nature of the endocrine disturbance has been established. Additional studies on the estrogen and

pregnandiol excretion in the urine over one or more cycles of such patients are desirable. Additional experimental evidence based upon the production of the various forms of mammary dysplasia in animals by administering various hormones is also required.

An objection often advanced against the conservative treatment of chronic cystic mastitis is that the lesion represents a precancerous condition (4). This opinion has not been substantiated in our work on mastodynia or cystic disease. There is evidence, however, to show that in cases of adenosis, the incidence of cancer of the breast is slightly higher than in normal individuals, 2% for adenosis and 0.6% for normal individuals (5). This objection may have some weight when estrogen therapy is used since mammary carcinoma in rats and mice has been produced by administering large doses of estrogen. This does not apply, however, to the use of progesterone which has been shown experimentally to be antagonistic to estrogen in this respect.

Two additional objections may be raised against endocrine therapy. First the results obtained are not permanent. While the symptoms regress, recurrence in a period of 18 months to 2 years is the rule. Second, spontaneous remission occurs frequently in mammary dysplasia and eventual disappearance of the disease is often observed in the absence of treatment.

In 166 cases of unilateral mastodynia with solitary tender nodules, followed for more than 5 years, 90% had reported disappearance of pain and tenderness within a period of 2 to 3 years, although no treatment of any kind had been instituted. However, in 62 bilateral cases with multiple tender nodules, 31 of the patients were unimproved after 3 or 4 years, one-third had persistent symptoms at the end of 8 years and at the end of 10 to 15 years, one-fourth had developed adenosis or Schimmelbusch disease. Endocrine therapy therefore is of value in bringing about remission in such cases and is an aid in preventing the development of adenosis, and may avoid needlessly mutiliating operations.

Among 99 cases of adenosis followed in which no treatment was advised 77 were traced beyond the 5-year period. Among these, 19 patients had persistent symptoms 5 to 11 years after the first examination, but 7 of these ultimately reported themselves well 8 to 22 years after the first examination. Five were ultimately treated with one or more excisions, one by amputation and two developed cancer of the breast. Endocrine therapy (progesterone injections) is indicated, in the author's opinion, in this group for the relief of symptoms. However, any definite nodule which is regarded as suspicious should be treated by excision and studied microscopically.

In cystic disease, in which a definite solitary nodule is the rule, excision permits pathologic verification of the diagnosis and in 75% of the cases additional cysts do not form after such treatment. Aspiration also may be used to confirm the diagnosis and in one-third of the cases so treated the cysts do not refill. Whether or not endocrine therapy is helpful in preventing recurrence after excision cannot be stated at this time.

The relief of symptoms observed in cases of mastodynia receiving injections of progesterone is apparently more prompt and requires fewer injections than when estrogen therapy is administered. In one case of severe mastodynia in whom previous estrogen therapy had failed to control symptoms, injections of progesterone were successful. In this case, however, the progesterone treatments have been given monthly since starting the treatment, pain and tenderness returning promptly if the injections are omitted.

In attempting to treat some of the patients in this series with doses of 10 mg. once weekly (instead of 5 mg. twice weekly) intermenstrual bleeding has been observed. In one patient the progesterone was implanted in the form of a pellet of 30 mg. This patient complained of uterine cramps in the premenstrum which she said resembled labor pains. Similar premenstrual cramps were observed in a patient receiving injections of progesterone in 10 mg. doses and in whom urinary pregnandiol determinations showed a normal pregnandiol excretion (58.5 mg. per cycle).

SUMMARY

Injections of progesterone (5 mg. in oil) were administered twice weekly for the last two weeks of one or two consecutive menstrual cycles in 27 patients with chronic cystic mastitis, including the subvarieties of mastodynia, adenosis and cystic disease. Relief of symptoms in cases of mastodynia and adenosis lasting 12 to 18 months was observed in most cases. In cystic disease the treatment is of doubtful value but may prevent recurrence following surgery or aspiration.

REFERENCES

1. Lewis, D. and C. F. Geschickter, *J. A. M. A.* 109: 1894, 1937.
2. Bucher, N. L. R., and C. F. Geschickter: *Endocrinology* 27: 727. 1940.
3. Bucher, N. L. R., and C. F. Geschickter: *Journal of Clinical Endocrinology* 1: 58. 1941.
4. Warren, S: *Surg. Gynec., Abst.* 71: 257, 1940.
5. Geschickter, C. F.: *Diseases and Tumors of the Breast*, J. B. Lippincott, Phila. In press.

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PSEUDOHERMAPHRODISM

PREGNANDIOL GLUCURONIDATE EXCRETION[1]

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IN 1929 MARRIAN (1) isolated pregnandiol from human pregnancy urine. Dingemanse, deJongh, Kober and Laqueur (2), and Butenandt (3) perfected the technic of the extraction and made further researches along these lines.

In 1936 and 1937 Venning and Browne et al. (4–10) elaborated a technic of gravimetric determination of sodium pregnandiol glucuronidate and showed that the excretion of this compound is associated with the activity of the corpus luteum, which produces progesterone during the luteal phase of the menstrual cycle and during pregnancy. According to Wilson and Randall (11) the determination of pregnandiol glucuronidate should have a place in the diagnosis of early pregnancy, especially in the presence of a missed period.

The above mentioned authors have shown that during the normal menstrual cycle appreciable amounts of pregnandiol glucuronidate begin to appear in the urine at about the twelfth premenstrual day of the cycle. The height of pregnandiol glucuronidate excretion corresponds to the height of corpus luteum activity from about the 15th to the 23rd day of the cycle. The amounts of pregnandiol glucuronidate excreted in 24 hours during that period range from 2 to 10 mg.

Unusually high levels of pregnandiol glucuronidate in the absence of pregnancy should be of interest to the medical profession, because of the close relationship, chemically and biologically, of pregnandiol to progesterone, testosterone and desoxycorticosterone. This close relationship has prompted the author to investigate the pregnandiol glucuronidate excretion in a case of pseudohermaphrodism.

CASE REPORT

L.S., a female, age 25 (fig. 1) a case of pseudohermaphrodism previously reported by the author (12) has been treated for primary amenorrhea, pseudohermaphrodism, and virilism at intervals since the age of 16.

During a pelvic exploratory operation performed because of pseudohermaphordism, she was found to have a somewhat hypoplastic uterus; tubes and ovaries were present; there were no abnormal growths or aberrant testicular tissue, and the palpation of the adrenals failed to reveal a tumor or an enlargment. The clitoris, the size of a normal penis, was amputated at that time.

Intensive estrogenic therapy subsequently used usually resulted in cyclical uterine bleeding; at one time a similar response was obtained by deep x-ray therapy to the region of the adrenals, administered by Dr. Milton Friedman (13). Later, however, the patient ceased to respond to either estrogenic or x-ray therapy, and it was thought advisable to follow the estrogenic therapy by intensive progesterone therapy. The following routine was, therefore, used: estradiol benzoate 50,000 R.U. was administered over a period of 2 weeks followed by progesterone, 30 mg.

Fig. 1. *L.S.*, AGE 25. Note hypertrichosis and masculine body configuration.

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[1] This case was presented as part of the exhibit during the Graduate Fortnight at the New York Academy of Medicine, November 1939.

in the latter 2 weeks of the cycle.[2] This therapy was carried out during April and May 1939.

Venning and Browne (14) found that 12 to 46% of injected progesterone could be recovered as pregnandiol glucuronidate in patients with an intact uterus. Stover and Pratt (15) were unable to recover any pregnandiol glucuronidate after injection of a corpus luteum extract. Hamblen, et al. (16), however, found that the injected progesterone not only failed to be converted into pregnandiol glucuronidate, but even caused a depression of spontaneous metabolism of the corpus luteum hormone.

The relation of pregnandiol glucuronidate excretion to progesterone therapy is illustrated in figure 2. As seen from this chart, the highest amount of pregnandiol glucuronidate excreted by this patient in 24 hours was 35.9 mg.; the lowest 12.4 mg. per 24 hours; the average excretion per 24-hour specimen was 20.7 mg. in the 6 determinations. Three and a half months after cessation of therapy, 25.8 mg. per 24 hours specimen was excreted; this amount as compared with the normal excretion present at the height of the corpus luteum activity in normal women is definitely elevated.

In view of the fact that Venning, Weil, and Browne (17) reported an elevated pregnandiol glucuronidate excretion in two cases of adreno-genital syndrome, it was thought advisable to repeat the pregnandiol studies on our patient, estimating the average daily output of pregnandiol glucuronidate for 15 consecutive days.

The combined specimens of urine from Jan. 1 to Jan. 10, 1940 inclusive were analyzed and showed that the average excretion (fig. 2) of pregnandiol glucuronidate was 21.9 mg. per 24 hours. The urine was again collected from Jan. 11 to Jan. 15 inclusive showing the daily average excretion of pregnandiol glucuronidate to be 29 mg. per 24-hour specimen. The patient did not receive any therapy for 8 months prior to or during this study.

Prior to these determinations an attempt was made to estimate subthreshold cyclical ovarian activity by means of vaginal smears over a period of one month. At no time, however, was there a frank follicular phase found. The smears were difficult to obtain, the vaginal orifice being infantile, the vagina dry, and the vaginal secretion scant and containing very few epithelial cells; round cells and leucocytes were predominant, therefore the increased excretion of pregnandiol glucuronidate in this patient has no relation to ovulation; the significance of the increased pregnandiol glucuronidate excretion in our case of pseudohermaphrodism is not clear.

Broster et al. (18, 19, 20) have demonstrated the presence of a hyperplasia of the androgenic zone of the adrenal cortex in patients presenting a clinical picture of adreno-genital syndrome; Hooker and Collins (21) demonstrated androgenic activity of desoxycorticosterone in capons, mice and rats; it is possible that the continuous and persistent elevation of pregnandiol excretion in our patient demonstrates that in her case, the pregnandiol glucuronidate excretion was not due to the progesterone therapy, but to some other undetermined cause, probably the hyperactivity of the adrenal cortex, particularly of the androgenic zone.

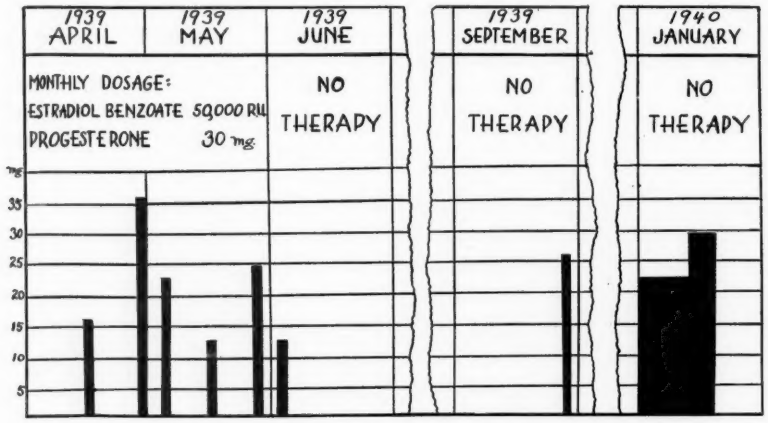

Fig. 2. Estimation of pregnandiol glucuronidate excretion in a case of pseudohermaphrodism. Note high levels of pregnandiol glucuronidate excretion in a case of pseudohermaphrodism; this level was unaffected by the administration of estrogenic and progesterone therapy. These endocrine substances were administered alternately for 2-week periods each.

[2] Estradiol benzoate (dimenformon benzoate) and progesterone (progestin) were supplied by Roche-Organon Inc. through the courtesy of Dr. Leo Pirk and Dr. B. L. Josephy.

Simultaneously with the pregnandiol glucuronidate studies in the above patient, three other primary amenorrhea patients with intact uteri were placed on the same type of therapy. Pregnandiol glucuronidate determinations carried out on these patients during therapy with progesterone in the same laboratories by the same technic did not yield any appreciable amounts of pregnandiol glucuronidate.

SUMMARY

Repeated pregnandiol studies in a case of pseudohermaphrodism revealed a persistently high level of pregnandiol glucuronidate excretion in the urine at varying periods. The average excretion without therapy was 25.5 mg. per 24-hour specimen, with therapy 20.7 mg. per 24-hour specimen.

This elevated excretion is apparently neither related to the therapy previously administered, nor to a possible early pregnancy.

The elevated pregnandiol excretion is probably an indication of excessive androgenic activity of the adrenal cortex of the patient herein reported.

Pregnandiol glucuronidate determinations in the presence of amenorrhea may be of diagnostic significance; high excretions of pregnandiol glucuronidate in the absence of pregnancy may suggest a diagnosis of a masculinizing tumor or a hyperplasia of the adrenal gland.

I am greatly indebted to Dr. B. L. Josephy and Dr. E. Schapiro of Roche-Organon Inc. for the pregnandiol glucuronidate studies in the case herein reported as well as the studies in three other cases of primary amenorrhea, and in one case of normal pregnancy.

REFERENCES

1. Marrian, G. F.: *Biochem. J.* 23: 1090. 1929.
2. Dingemanse, E., S. E. deJongh, S. Kober and E. Laquer: *Deutsch. Med. Wchnschr.* 56: 301. 1930.
3. Butenandt, A.: *Ber. d. Deutsch. chem. Gesellsch.* 63: 659. 1930; 64: 2529. 1931.
4. Venning, E. and J. S. L. Browne: *Proc. Soc. Exper. Biol. & Med.* 34: 792. 1936.
5. Venning, E. and J. S. L. Browne: *Am. J. Physiol.* 119: 417. 1937.
6. Venning, E. and J. S. L. Browne: *Endocrinology* 21: 711. 1937.
7. Venning, E., J. S. Henry, and J. S. L. Browne: *Canad. M. A. J.* 36: 83. 1937.
8. Browne, J. S. L., J. S. Henry, and E. Venning: *J. Clin. Invest.* 16: 678. 1937.
9. Venning, E. H.: *J. Biol. Chem.* 119: 473. 1937.
10. Venning, E. H.: *J. Biol. Chem.* 126: 595. 1938.
11. Wilson, R. B. and L. M. Randall: *Proc. Staff Meet. Mayo Clin.* 14: 8. 1939.
12. Finkler, R. S.: *J.A.M.A.* 102: 924. 1934.
13. Finkler, R. S. and M. Friedman: *Endocrinology* 22: 104. 1938.
14. Venning, E. H. and J. S. L. Browne: *Am. J. Physiol.* 123: 209. 1938.
15. Stover, R. F. and J. P. Pratt: *Endocrinology* 24: 28. 1939.
16. Hamblen, E. S., W. K. Cuyler, N. B. Powell, C. Ashley and M. Baptist: *Endocrinology* 25: 13. 1939.
17. Venning, E. H., P. G. Weil, and J. S. L. Browne: *J. Biol. Chem.* 188: cvii. 1939.
18. Broster, L. R., H. Gardiner, and J. G. Greenfield: *Brit. J. Surg.* 19: 557. 1932.
19. Broster, L. R. and H. W. C. Vines: London, H. K. Lewis, 1933.
20. Broster, L. R. and H. W. C. Vines: *Brit. M. J.* 1: 662. 1937.
21. Hooker, C. W. and J. J. Collins: *Endocrinology* 26: 269. 1940.

Therapeutic Symposium

Androgen Therapy in the Human Female

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The therapeutic use of androgens for gynecologic disorders is the outgrowth of the observations by biochemists, physiologists and clinicians concerning the presence and role of the normally occurring androgens in the female. Koch and Gallagher identified substances in the testicles of bulls and David and Laqueur separated an androgenic compound called testosterone from the same source. Later it was produced synthetically by Butenandt and Ruzicka. Koch reported the presence of 4 androgenic substances in the human urine but could not isolate testosterone. One of these four androgens was androsterone which Butenandt and Tscherning were able to crystallize. Later, the Callows identified androsterone and dehydroandrosterone in the urine of normal women. They found androgens even in puberty, though in small amounts varying from 1.1 to 3 international units. Gallagher et al. stated that normal young women excrete 26 I.U. of androgen daily in the urine and men excrete 40 to 56 I.U. Only traces were found before puberty. Koch suggested that the adrenal probably was the source of the androgens in the female. Hill believes that the ovaries may secrete male hormone as he was able to show that ovaries transplanted to the ears of castrated mice stimulated the seminal vesicles and prostate. He believed that the temperature of the environment played a part. Hill and Strong further suggested that the male hormone secreted by the ovaries differed chemically from testicular androgens but acted similarly. Koch suggested that the androgens might be physiologically important in women. With the discovery of androgenic compounds in the urine of normal, adult females, it seems likely, as Koch suggested, that the androgens might play a part in the female economy and immediately numerous investigations were undertaken and reported concerning the physiologic activity in the human female of various androgenic compounds. It was noted that the amount of androgenic activity present in the prepubertal female was small and so it was believed that the principal role of the androgens would be played in the sexually mature woman. It was soon noted that testosterone was more active than any of the androgenic compounds found in the urine. Testosterone propionate was reported as the most active androgen by Parkes and by Deanesly and Parkes, as well as by Miescher, Wettstein and Tschopp.

Korenchevsky stated that the female sex system was stimulated in varying degrees by androgenic substances. He found that testosterone propionate was most active and then, in a descending scale, testosterone, androstanediol, androstenediol, androstenedione, transdehydrostene and androsterone.

Effects on Estrus, Ovary and Pituitary

The effects of androgen action on the female vary. In some instances, it has an estrin-like action, in others a progestin-like action and, at times, there seems to be a definite anti-estrin activity. The future will decide just when and under what particular conditions these various properties are predominant.

Ihrke and D'Amour showed that the estrous cycle in rats was suppressed by administering extracts of bulls' testes. Robson obtained the same results in mice and Browman in rats. Hartman suppressed menses in monkeys following the injection of testosterone propionate and Engle and Smith inhibited the estrin-deprivation bleeding in 4 adult castrated monkeys. Courrier and Cohen, using testosterone acetate, obtain follicular inhibition and a resulting absence of estrus. Estrus was also inhibited, experimentally, by Nelson and Merckel. Parkes, in regularly cyclical mice, also reported the inhibition of estrus. However, when the androgen used in the former experiment (testosterone propionate) was combined with estrone, estrus was not abolished. This observation

was corroborated by Selye, Browne and Collip. Kochakian showed that in mice the estrogens and androgens were antagonistic to a limited extent. Inhibition of ovulation has been observed in animals after treatment with androgens by Zuckerman and Cotte et al. In the human being, Gaines, Salmon and Geist, because of the endometrial changes following treatment with testosterone propionate, concluded that ovulation was inhibited. Salmon showed that in a human female castrate 815 mg. of testosterone propionate given for 27 days inhibited the pituitary. This has been corroborated by Shorr, Papanicolaou and Stimmel, Nathanson and Towne and by Laroche et al., using testosterone propionate. In rats, Hamilton and Wolfe made similar observations. Hertz and Meyer reported pituitary inhibition in parabiotic rats using testosterone, testosterone propionate and dehydroandrosterone. In a large number of unpublished experiments on post-menopausal women treated with testosterone propionate, we have obtained a definite inhibition of the urinary gonadotropic hormone output. Huffman and Bos have shown that the inhibition of ovulation is not due to the direct action of testosterone propionate on the ovary but indirectly to the depressing effect on the pituitary. The above quoted observations seem to indicate that the androgens may inhibit the action of the estrogens in three ways: *a*), directly; *b*), by their action on the ovary; *c*), by depressing the pituitary; or, possibly, by all three.

Effects on Endometrium and Cyclical Bleeding

Other effects following the administration of androgens to women have been obtained in further substantiation of the views already expressed. In the human being it has been shown (Gaines, Salmon and Geist) that the endometrium of a normal cyclical female can be reduced to a condition of atrophy, possibly as the result of indirect action on the ovary with inhibition of ovulation (unpublished experiments). In addition to the effects on estrus, ovulation and cyclical bleeding in animals, the cyclical menses in the human being have been inhibited (Geist, Salmon and Gaines, and Papanicolaou, Ripley and Shorr).

Effects on Vagina, Myometrium and Tubes

On the vagina, contradictory effects have been noted. In most instances, the normal vaginal mucosa and smear have undergone a regression while, on the other hand, a few reports have stated that the post-menopausal vaginal smear has been restored to normal. This seems to indicate a double action, one resulting in a response similar to an estrin stimulation and a second effect resulting in an estrin inhibition. Salmon, in the treatment of a human female castrate, was able to change the negative vaginal smear to a positive. Nathanson and Towne confirmed this observation. However, Shorr, Papanicolaou and Stimmel, as well as Rothermich, could not obtain the same result. Papanicolaou, Ripley and Shorr reported a case treated with 775 mg. of testosterone propionate in which they were able to transform the positive vaginal smear to a negative one. Salmon, Walter and Geist were able to convert the normal smear to an estrogen deficiency type in normal cyclical women with 500 mg. of testosterone propionate. They also noted that with the disappearance of the large cornified cells and the predominance of the 'atrophy' cells, the glycogen usually present in the normal smear receded and at times disappeared completely. The glycogen began to reappear with the return of the normal cell types.

Breast Action

The effect of androgens on the breasts and on lactation has also been investigated by groups of workers and some therapeutic suggestions have been made as a result of their studies. Cotte, Martin and Miliff state that in rabbits, following estrin treatment, the androgens cause a development of the gland structure of the breast. Selye and his collaborators describe a similar reaction associated with milk production in rats when large doses are employed, without the preliminary stimulation with estrin. However, there is no response in the hypophysectomized animal, i.e., the action is indirect through the stimulation of the pituitary. Robson and also DeJongh demonstrated that in mice lactation is suppressed and Kurzrok and O'Connell confirmed this in human beings, as did Birnberg, Kurzrok and Klor, Siegel and Silverstein and Beilly and Solomon.

In further confirmation of the many sided activities of the androgens, Korenchevsky, Dennison and Simpson found that the vestigial male organs in the young female animal could be stimulated by administering androgens and Butenandt and Kudzus found that androgens caused premature opening of the vagina in immature rats. Salmon demonstrated that testosterone had a bisexual action in the immature rat, stimulating follicle growth and corpora lutea formation in the ovaries, hypertrophy of the vagina and uterus and growth of the clitoris and preputial glands. He also showed that testosterone had a direct action on the Müllerian tract since it stimulated growth of the uterus and vagina in castrated immatures. Nathanson, Franseen and Sweeney showed that the gonadotropic effect in the immature rat ovary was mediated through the hypophysis.

Progestin-Like Action

A progestin-like action on the uterus of castrated rabbits was described by Klein and Parkes. Koren-

chevsky et al., were able to produce progestational effects on the endometrium of the rat. It was noted by Robson that it inhibited the contractions of the uterus in rabbits and by Geist, Mintz and Salmon that it abolished the tubal contractions in normally cyclical women. As further evidence of its progestin-like action may be mentioned the observations of Leonard, Sager and Hamilton, Green and Burrill, and Scipiades, all of whom were able to maintain gravidity in the castrate rat by injecting androgens.

The effect of androgens on the uterus and its lining apparently varies. In the human being we were unable to obtain a progestational response in the endometrium primed with adequate estrin (unpublished experiments). Loeser reported endometrial atrophy following the injection of testosterone propionate. This too has been reported by Gaines, Salmon and Geist. The inhibition of the menses for as long as 2 to 6 weeks may accompany such regression due presumably to a local effect, a pituitary inhibition, or the direct neutralization of the circulating estrin. Zuckerman and Hartman inhibited the menses in monkeys, Engle and Smith inhibited the estrin-deprivation bleeding likewise in the monkey, though they did not produce an endometrial atrophy, and Geist, Salmon and Gaines and Papanicolaou, Loeser and Foss inhibited the menses in the human being. Lipschutz and his coworkers were unable to stimulate uterine growth unlike the reaction from estrin stimulation in castrate human females, whereas Courrier and Gros found the testosterone propionate acted on the myometrium causing a uterine hypertrophy.

Metabolism

The metabolism of androgens in the human body is as yet little understood. It is suggested that the ovary may produce androgens, for we do know that the ovaries contain male elements that at times give rise to tumors associated with virilism, and Hill has shown that ovaries transplanted to the ears of rabbits can produce androgens. Nevertheless, most observers are of the opinion that the adrenals really are the organs most concerned in the production of androgens in the female. Koch pointed out that in females with hypertrichosis, urinary androgen excretion was definitely higher than in normal women.

Testosterone is not found in the female but androsterone and dehydroandrosterone are present in the urine. They are much less active than testosterone and probably represent degradation products. Hamblen failed to note a variation in the androgen output after hysterectomy and bilateral oophorectomy. Nathanson et al., were unable to demonstrate an increase in the androgen content of the urine following the administration of testosterone propionate. They suggested that possibly the androgens were converted into estrogens in the body. Kochakian recovered only 2 to 6% of the administered androgens and likewise suggested their conversion into estrogen, or possibly into an inactive form of androgen. Zondek had made the same suggestion in 1934. Dorfman and Hamilton, however, noted a somewhat higher urinary androgenic titer in females treated especially by the intramuscular route. They also noted some intestinal absorption when the oral route was utilized, which observation raises the hope of possibly obtaining an active oral preparation. Hamilton and Dorfman stated that implanting testosterone propionate crystals was the best method of administration. We have utilized both implants of crystals and pellets and have found them clinically of no benefit in women. These observations will be reported in detail in another publication.

From this vast accumulation of data, some corroborative, some contradictory, it is difficult to formulate definite concepts concerning the action of the androgens in the female. The future must clarify the subject and reconcile the differences. It seems evident that certain facts are definite. Androgens do occur in the female normally, they can inhibit the pituitary, they can either directly or indirectly through the pituitary inhibit the ovary and in all probability they can negate the actual circulating estrin. Because of these biological effects, attempts have been made to obtain clinical cures (in the female) of certain abnormal conditions presumed to be related to disturbances of the normal endocrine balance.

It must be remembered that the endocrine disturbances underlying the conditions for which androgens are to be employed are not clearly understood and so to a great extent this therapeutic venture is empirical. The abnormalities that seemed to fall into the most promising group are: functional meno-metrorrhagia, functional dysmenorrhea, mastalgia and mastopathies and pre-menstrual tension. Other pathological variations have been treated but the results to date have not been sufficiently definitely correlated to permit judgment of their worth.

ANDROGEN THERAPY

Functional Bleeding

The overwhelming evidence of suppression, inhibition and negation of estrogenic activity by the androgens immediately suggested that the therapeutic administration of these latter substances might be of value in those abnormal conditions presumably due to, or associated with, excessive estrogen action. The so-called functional meno-metrorrhagia presented a seemingly ideal field for therapeutic trial. Hamblen et al. failed to find a change in the androgen output in these cases.

Loeser treated 20 cases and succeeded in inhibiting the menstrual periods for 8 to 10 days after the injection of 300 mg. of testosterone propionate. The inhibition could be extended to a month or longer with doses up to 600 mg. As much as 1500 mg. was given with no untoward effect and the menses returned after cessation of treatment. Foss confirmed Loeser's results and Geist, Salmon and Gaines treated 25 cases with excellent results in the majority of them. A larger series will be discussed later. Demarest and Mme. Capitain likewise had good results from the treatment of menstrual irregularities using both testosterone propionate and testosterone acetate. Mazer and Mazer used larger doses (450 to 1000 mg. per month) with good results. They reported that in some cases pregnancy occurred in from 1 to 10 months after cessation of therapy. Sturgis, Abarbanel and Nader obtained good results in 12 cases with total doses as low as 10 to 120 mg. in individual doses of 10 to 30 mg. We have not been successful in relieving the condition with such small amounts and in no case did we feel that the immediate cessation of bleeding resulted from medication administered during a bleeding episode.

The series of cases treated by Geist, Salmon and Gaines (unpublished data) now totals 60 cases, 15 of which had small fibroids. The results on the whole were very favorable. Of 45 cases not associated with fibroids, the late results showed an absolute failure in only 3 cases and a moderate improvement in 12. Normal menses were established and maintained for 2 years in 26 cases. The clinical improvement was correlated with definite changes in the endometrium as revealed by suction biopsies performed at stated intervals before, during and after treatment. The above authors have shown in previous communications that the administration of adequate doses of testosterone propionate causes striking morphologic changes in the endometrium of regularly menstruating women. These changes consist of an abolition of the secretory phase and an inhibition of the proliferative phase progressing to atrophy, with a suppression of the menses. All the cases treated were carefully examined and pelvic disease was excluded, other than the small fibroids found in the 15 cases already mentioned. The duration of treatment varied from 2 to 24 months. Fifty per cent of the patients were between the ages of 40 and 49 years. The others varied between 24 and 39 years. The duration of the abnormal bleeding varied from 2 months to 10 years with an average of 2 years.

Dosage. In the early part of the investigation, because of our uncertainty regarding the optimal dose, we started with amounts varying from 45 to 500 mg. per month. Some investigators have advised doses as small as 25 to 50 mg. per cycle (Beclere, Evelbauer). In some of our cases the total dosage was as much as 1000 mg. per month. The highest dosage given any single case was 2150 mg. over a period of 3 months. We have since learned that such large doses are unnecessary and to-day we find that in most cases from 300 to 400 mg. per cycle is adequate.

Preliminary endometrial biopsies were obtained premenstrually when possible to determine the presence of a corpus luteum effect. At regular intervals additional biopsies were obtained during the period of bleeding and during other phases of the cycle. In the majority of cases the abnormal bleeding occurred from a secretory endometrium. In only 8% was the bleeding associated with a hyperplastic endometrium.

Clinical results.

Forty-five Cases of Functional Bleeding

Primary Results	
Temporary amenorrhea	29 cases
Normal menses	15 cases
Moderate improvement	1 case
Late Results (2 year follow-up)	
Normal menses	26 cases
Hypomenorrhea	3 cases
Amenorrhea	1 case (at menopause age)
Moderate improvement	12 cases
Failures	3 cases

Fifteen Cases Associated with Small Fibroids

Primary Results	
Temporary amenorrhea	4 cases
Normal menses	9 cases
Moderate improvement	2 cases
Late Results	
Normal menses	6 cases
Moderate improvement	2 cases
Failures	7 cases

It is evident that the results in cases of bleeding associated with small fibroids are not as satisfactory as when no complicating lesion is present. It may be noted that there was no discernible diminution in the size of the fibroids.

The question of the modus operandi is difficult to answer. Frankly, we do not know. There is evidence to show that the androgens inhibit estrus in the rodents, ovulation and menses in the monkey and in human beings. The androgens also depress or inhibit the action of the anterior pituitary. It would seem possible from the previous experimental work quoted that the clinical effects may be the result of inhibition of the pituitary which suppresses the normal ovulatory cycle. There is also the possibility of direct negation of the normal estrin content, or theoretically of establishing a normal estrin-androgen balance.

After discontinuation of treatment the normal ovulatory cycle returns and in 60% of the functional bleeding cases the condition is markedly improved. How long this state may be maintained is a problem for the future. Our follow-up has demonstrated good results for as long as 22 months.

Dysmenorrhea

Functional dysmenorrhea is a broad term but under it is classed a series of symptoms associated with the menses, such as severe cramps immediately preceding, during, or immediately after the menses and not associated with definite palpatory evidence of disease in the pelvis. This symptom complex suggested itself as a possible field for exploration to determine whether androgen therapy might be of value in view of the depressant effects of androgen administration on the contractility of tubal and uterine musculature.

Dysmenorrhea does not represent, in all probability, a single entity. It is really a symptom complex which may be associated with many and varied etiologic factors. Until we learn to classify and recognize the various types there will naturally be a certain proportion of failures with any single method of treatment applied to the entire group. Briefly, there are 3 current theories of the etiology of dysmenorrhea: *a*), a deficiency of progesterone permitting the unopposed action of estrin upon the uterine muscle; *b*), an excessive estrin production resulting in an exaggeration of the normal uterine contractility and *c*), excessive progesterone activity (Cannon, Lackner, Krohn, and Soskin). We have proceeded on the theory that the inhibition of the pituitary with consequent suppression of ovulation and inhibition of estrin and corpus luteum formation and the inactivation of the circulating and stored estrin by androgens might relieve the condition (Salmon, Geist and Walter). In the treatment of 30 cases the following results were obtained.

Early Results

Complete relief	22 cases
Incomplete relief	4 cases
Failures	4 cases

Results after 24 months (25 cases)

Complete relief (3 to 24 months after treatment)	14 cases
Incomplete relief (2 to 24 months after treatment)	8 cases
Failures	3 cases

One or two menstrual periods were suppressed in 9 cases but returned to normal after discontinuation of the treatment and with relief of symptoms.

It is interesting to note that all the cases treated had pre-treatment secretory endometria indicating ovulation and corpus luteum formation. During treatment, the secretory phenomena in the endometrium were absent, indicating an inhibition of progesterone formation. In some cases there was definite estrin inhibition as indicated by the endometrial biopsies and vaginal smears. This inhibition promptly ceased after cessation of treatment with the return of a normal menstrual rhythm and relief of symptoms. To obtain complete inhibition, a dose of 500 to 900 mg. in a single cycle, starting not later than the sixth day of the cycle, was given. Subsequent studies revealed that such high dosage is not necessary to obtain symptomatic relief. The vaginal smears showed evidence of regression with doses of 350 mg. per cycle and gradually return to normal in from 1 to 3 weeks following cessation of treatment. The relief of symptoms at times took place before the evidence of regression in the vaginal smear, indicating that satisfactory clinical results can be achieved with doses smaller than that necessary to cause a regressive smear or a hypoplastic endometrium. The smear changes are important to stress because they offer an indicator for the control of dosage and the avoidance of by-effects.

The mechanism of the action of testosterone is difficult to explain because we do not know the etiology of dysmenorrhea. The androgens play an important role in the hormonal organization of the normally menstruating woman, perhaps as a balance or mediator of the physiologic effects of the ovarian hormones. Speculatively, one might venture to suggest that an androgen deficiency may exist in some types of dysmenorrhea, permitting an unopposed or unmodified estrin activity. This is supported to an extent by the evidence already presented of the antagonism between androgens and estrogens in the human female. Quantitative studies of androgen and estrin balance in functional dysmenorrhea may help elucidate this problem.

The literature on the use of androgens in dysmenorrhea is scanty. Rubenstein and Abarbanel reported 26 cases in whom 16 were cured and 4 improved. They utilized small doses of 5 mg., given 2 or more times before the expected flow and suggested that the good results were due to the progesterone-like action of the testosterone propionate. We were unable, in our cases, to obtain relief with such small dosage.

Mastopathies and Premenstrual Mastalgia

Because of the effects noted in the breasts of experimental animals treated with androgens, and of the presumed estrogen disturbance associated with premenstrual mastalgia and true mastopathia, these pathologic conditions of the breasts have been treated with androgens. Premenstrual mastalgia is a term applied to the regularly recurring pain in the breasts or breast associated with a sense of fullness, tenderness, pain in the nipple and some temporary enlargement, the result of vascular changes and edema. At times the breast may feel somewhat irregular to the palpating fingers. A similar condition not associated with the premenstrual phase may be found especially in women near the menopause, and in these patients the breasts may present nodules and small cysts. Loeser caused reduction in the size of such breasts and relief from pain in 2 cases with 600 mg. of testosterone propionate. Demarest treated premenstrual breast congestion by administering testosterone acetate before

ovulation. In 37 cases good results were reported. The first injection was given 10 days after the onset of the period and then given every 2 to 4 days until a day or two before the expected period, using 5 to 10 mg. per injection. Similar good results were obtained by Demarest and Capitain using testosterone acetate. In 16 cases treated by Spence, 14 were relieved after injections of 25 to 50 mg., for a total of 100 to 3000 mg. Guerica treated 4 cases of acute puerperal mastitis and one chronic case. He gave 50 to 250 mg. in a period of 4 days. The pain and inflammation were relieved and in the chronic case with a lacteal fistula, following the administration of 50 mg.every day for 4 days, lactation ceased and the fistula healed. Kurzrok and O'Connell, employing 25 mg. doses of testosterone propionate twice a day, were able in 2 days to cause inhibition of lactation. Birnberg, Kurzrok and Klor inhibited lactation in the puerperium in 49 of 56 cases, using a total of 125 to 150 mg. of testosterone propionate and Siegler and Silverman, in 50 cases, inhibited lactation in the puerperium in 47. They gave 3 doses of testosterone propionate of 10 mg. each. Beilly and Solomon also had good results in 58% of their cases using 10 to 125 mg. in 1 to 4 injections.

Our own results in an unpublished series of 14 cases, 10 of whom complained of premenstrual pain, showed 6 relieved after a total of 250 mg. of testosterone propionate given in the latter half of the cycle. Four cases presented cystic nodular painful breasts and of these 2 were relieved after total doses of 350 mg. given over a period of one month. The follow-up in these cases has been too short to make definite claims for the treatment. Such cases should, if possible, be controlled by breast biopsies.

Premenstrual Tension

The above condition was described and named by Frank and is associated with complaints of nervousness, irritability, a feeling of tension and unrest preceding the onset of the menses. He believed it was associated with a hyperestrinemia. In a group of 20 such cases studied by Dr. U. J. Salmon and myself testosterone propionate was given in doses up to 200 mg. administered in the last 2 weeks of the cycle. Thirteen cases were subjectively relieved from 6 months to 2 years after cessation of treatment. In 5 cases there was a recurrence of some symptoms after 6 months and in 2 cases complete failure. This too is a fruitful field for further investigation.

Menopause Syndrome

It would seem strange to suggest that the distressing symptoms of the menopause might be relieved by the administration of testosterone especially as Hamblen et al. have pointed out that the output of androgens in the menopausal woman is extremely high. Because of the estrin-like action, at times, of the androgens, they have been utilized. Salmon first pointed out that the administration of testosterone propionate in the menopausal woman relieved the symptoms, inhibited the pituitary and converted a negative vaginal smear to normal. Shorr, Papanicolaou and Stimmel confirm these findings except that they were unable to produce a reversal of the smear. Nathanson and Towne obtained improvement in 4 human female castrates using 112.5 to 242.5 mg. over a period of 4 to 6 weeks. They confirmed all the findings of Salmon. They also noted that an increased amount of androgen was not present in the urine and suggested that the androgens were converted into estrogens in the body because they found an increase in the urinary estrogens. Birnberg, Kurzrok and Livingston found that the menopausal symptoms in three castrated women were improved but that the endometrium was not affected. In a later paper by Kurzrok, Birnberg and Livingston they reported a group of 21 cases of natural and artificial menopause treated by injections of 25 mg. of testosterone propionate twice weekly. Of these, 80% were improved in 2 to 3 weeks. Then 30 to 40 mg. doses weekly kept the symptoms under control. The smears were not affected and there was no itching or dryness of the vagina. In these cases, vaginal bleeding took place and in one of these the endometrium was in an early proliferative phase. Laroche, Simonnet and Bompard also reported good results in the treatment of 18 cases of the menopausal syndrome using testosterone propionate or acetate.

In collaboration with Dr. Salmon, a group of 35 cases of the menopausal syndrome were treated with 25 to 50 mg. of testosterone propionate three times weekly (the details to be reported later). In this selected group there was a definite alleviation of symptoms noted as early as the second week. As much as 2000 mg. was given as a total dosage. In only a few cases were the symptoms completely relieved. The recurrence of symptoms was rapid, usually within 1 to 2 weeks after discontinuation of the treatment. Its value in the menopause is very limited but it may be employed in the small group that is resistant to estrin therapy or that is associated with bleeding.

During the course of our menopause studies, we observed that a number of cases that had suffered from impairment of hearing, tinnitus and head noises were greatly improved by testosterone therapy. The mechanism of this therapeutic effect is difficult to explain at present.

Arrhenomimetic Effects

Caution must be urged in the use of the androgens in gynecological disorders. While the androgens do occur in the urine of normal women, yet the exhibition of these substances to female patients, unless

carefully controlled, may produce by-effects mainly of an arrhenomimetic character. There appears to be a normal androgen-estrogen balance which may be disturbed by administering the androgens in too large quantity. Determination of the exact relations must be the work of the future. As is true of most active drugs, there is a therapeutic as well as a toxic dose. The therapeutic dose should not be exceeded except under unusual circumstances. Loeser (quoted by Foss) reported one case of hoarseness and Foss noted enlargement of the clitoris (not a serious by-effect) in a case treated with doses up to 2200 mg., from 3 to 8 weeks. Salmon, Geist and Walter reported 26 cases treated with testosterone propionate for functional dysmenorrhea and described arrhenomimetic changes, viz., hirsuties, hoarseness, slight clitoral enlargement and atrophic vaginitis. It was noted that brunettes with a tendency to hirsutism seemed to be more susceptible especially to an increased hirsutism. This observation has recently been confirmed by the work of Hamblen et al. Koch noted that in the normal woman the estrogen excretion was higher than the androgen output. In hypertrichosis, this ratio was reversed. In most instances the by-effects regressed markedly or completely disappeared after the cessation of treatment. A subsequent report will be published dealing with this aspect of the use of androgens in a series of 171 cases. We must realize that there are harmful potentialities in the use of any drug unless specific indications and controls are observed. We know the tolerance threshold and the objective criteria resulting from adequate therapeutic dosage for androgens, i.e., vaginal smear changes, vaginal and uterine epithelial response. Greenhill and Freed recently reported 2 cases of arrhenomimetic effects. Mazer and Mazer likewise reported 2 cases with hirsutism and 2 with voice changes following androgen therapy. In our study of 171 cases treated with testosterone propionate we were able to establish a tolerance threshold which, if not crossed, did not result in arrhenomimetic effects except in isolated instances of individual susceptibility.

Another common finding, not tabulated because our observations are not complete, is a rapid weight gain. It is probably related to the retention of nitrogen, electrolytes and water (Kenyon, Knowlton, Sandiford, Koch and Lotwin). A marked increase in libido is also manifested following therapy, which rapidly returns to normal for the individual with cessation of the treatment.

The total dosage is not the only factor that must be evaluated in our attempt to control the by-effects. The individual tolerance, the age of the patient and the inherent tendency towards virilism all play a role. These factors must be kept in mind as well as the careful checking of the vaginal changes, accurate clinical observation of the patient and strict adherence to the tolerance threshold. Below a total dosage of 300 mg. per month, we are practically safe from arrhenomimetic effects and those that do occur disappear after cessation of treatment.

A. TOTAL CASES TREATED AND RESULTS

No. of cases	Dosage	Voice changes		Hirsuties		Acne		Clitoral enlargement	
	mg.	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
25	300 or less	1	4	2	8	5	20		
55	300–600	6	11	4	7	2	4		
79	600 or less	7	8	6	8	7	9		
92	600–3000	22	24	17	18	7	8	3	3
171	all doses	29	17	23	11	14	8	3	2

B. ANALYSIS OF THE CASES WITH BY-EFFECTS

Dosage	No. of cases	Voice restored to normal	Very slight huskiness	Slight to moderate improvement	Follow-up
mg.					
300 or less	1		1		
300–600	6	3	1	1	1
600–3000	22	13	2	7	0

Methods of Administration

The methods of administration that we have employed are the intramuscular injection of testosterone propionate in oil, in doses from 5 to 50 mg. per injection, the implantation of crystals and pellets and the oral administration of methyl testosterone. We have implanted, subcutaneously, 9 cases suffering from functional bleeding and dysmenorrhea utilizing 25 to 50 mg. of crystalline testosterone propionate. There was no therapeutic relief or objective evidence of effective absorption. We have also implanted, subcutaneously with pellets, 9 cases of which 8 were functional bleeding and 1 a menopausal syndrome. The pellets contained from 150 to 500 mg. of testosterone propionate. There was no therapeutic effect and in the short time under observation no evidence of effective absorption. The results of these experiments will be reported subsequently. The oral route to date has proved unsatisfactory.

CONCLUSION

Testosterone propionate or acetate apparently are substances that have a place in the therapy of certain gynecologic disorders of endocrinopathic origin. It is still too early in this stage of the investigations to assign a definite place to this therapeutic agent. There seems to be a clear cut rationale for its use in many conditions. The future must assign the position to be occupied by androgen therapy in the female.

REFERENCES

BECLERE, C.: *Bull. Soc. de Gynec. et d'Obst.* 27: 745. 1938.
BEILLY, J., AND S. SOLOMON: *Endocrinology* 26: 236. 1940.
BIRNBERG, C. H., L. KURZROK, AND S. KLOR: *Am. J. Obst. & Gynec.* 39: 107. 1940.
BROWMAN, L. G.: *Proc. Soc. Exper. Biol. & Med.* 36: 205. 1937.
BURRILL, M. W., AND P. GREENE: *Proc. Soc. Exper. Biol. & Med.* 42: 764. 1940.
BUTENANDT, A., AND J. HANISCH: *Ztschr. f. Physiol. Chem.* 237: 89. 1935.
BUTENANDT, A., AND H. KUDZUS: *Ztschr. f. Physiol. Chem.* 237: 75. 1935.
BUTENANDT, A., AND K. TSCHERNING: *Ztschr. f. Physiol. Chem.* 229: 161. 1934.
CALLOW, N. H., AND R. K. CALLOW: *Biochem. J.* 32: 1759. 1938.
CANNON, J. D.: *J. Obst. & Gynec. Brit. Emp.* 43: 492. 1936.
COTTE, G. J., F. MARTIN, AND E. MANKIEWICZ: *Gynecologie* 36: 561. 1937.
COTTE, G. J., F. MARTIN, AND MILIFF: *Gynecologie* 38: 257. 1939
COURRIER, R., AND S. G. COHEN: *Compt. Rend. Soc. de Biol.* 124: 925. 1937.
COURRIER, R., AND G. GROS: *Compt. Rend. Soc. de Biol.* 127: 921. 1938.
DAVID, K., E. LAQUEUR, E. DINGEMANSE, J. FREUD, AND S. DE-JONGH: *Acta. Brev. Neer. de Phys.* 5: 4, 52, 84. 1935.
DAVID, K.: *Acta. Brev. Neer de Phys.* 5: 85. 1935.
DEANESLY, R., AND A. S. PARKES: *Biochem. J.* 31: 1161. 1937.
DEJONGH, S. E.: *Acta. Brev. Neer.* 3: 52. 1933.
DEMAREST: *Semaine d. Hôp. de Paris* 14: 251. 1938.
DEMAREST and CAPITAIN: *Presse Med.* 45: 777. 1937.
DEMAREST AND CAPITAIN: *Presse Med.* 46: 185. 1938.
DEMAREST AND CAPITAIN: *Presse Med.* 45: 1109. 1937.
DORFMAN, R. J., AND J. B. HAMILTON: *J. Clin. Invest.* 18: 67. 1939.
EHRENFEST, H.: *Am. J. Obst. & Gynec.* 34: 530, 699, 1051. 1937.
ENGEL, E. T., AND P. E. SMITH: *Endocrinology* 24: 1. 1939.
EVILBAUER, K.: *Münch. Med. Wchnschr.* 86: 126. 1939.
FLUHMAN, F. C.: *Endocrinology* 23: 193. 1938.
FOSS, G. L.: *Lancet* 1: 992. 1938.
FOSS, G. L.: *Lancet* 1: 502. 1939.
FRANK, R. T.: *Arch. Neurol. & Psychiat.* 26: 1053. 1931.
GAINES, J. A., U. J. SALMON, AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 38: 779. 1938.
GALLAGHER, T. F., D. H. PETERSON, R. I. DORFMAN, A. KENYON, AND F. C. KOCH: *J. Clin. Invest.* 16: 695. 1937.
GEIST, S. H., M. MINTZ, AND U. J. SALMON: *Proc. Soc. Exper. Biol. & Med.* 41: 556. 1939.
GEIST, S. H., U. J. SALMON AND J. A. GAINES: *Endocrinology*, 23: 784. 1938.
GREEN, R. R., AND M. W. BURRILL: *Proc. Soc. Exper. Biol. & Med.* 42: 582. 1939.
GREENHILL, J., AND S. FREED: *J.A.M.A.* 112: 1573. 1939.
GUERICA, F.: *Atti. d. Soc. Ital. Obst. & Ginec. Rome*, 35: 353. 1939.
HAMBLEN, E. C.: *Endocrinology* 25: 491. 1939.
HAMILTON, J., AND R. I. DORFMAN: *Endocrinology* 24: 71. 1939.
HAMILTON, J., AND J. M. WOLFE: *Endocrinology* 22: 360. 1938.
HARTMAN, C.: *Proc. Soc. Exper. Biol. & Med.* 37: 87. 1937.
HERTZ, R., AND R. MEYER: *Endocrinology* 25: 520. 1939.
HILL, R. T.: *Endocrinology* 21: 497. 1937.
HILL, R. T., AND M. T. STRONG: *Endocrinology* 22: 663, 1938.
HUFFMAN, J. W., AND L. BOS: *Endocrinology* 26: 259. 1940.
IHRKE, I. A., AND F. E. D'AMOUR: *Am. J. Physiol.* 96: 289. 1931.
KENYON, A. T., K. KNOWLTON, I. SANDIFORD, F. C. KOCH, AND G. LOTWIN: *Endocrinology* 26: 26. 1940.
KLEIN, M., AND A. S. PARKES: *Proc. Roy. Soc. London* 21: 574. 1937.
KOCH, F. C.: *Bull. N. Y. Acad. of Med.* 14: 655. 1938.
KOCH, F. C.: *Harvey Lectures* 1937 to 1938.
KOCH, F. C.: *J. Urol.* 35: 382. 1938.
KOCHAKIAN, C. D.: *Endocrinology* 23: 463. 1938.
KOCHAKIAN, C. D.: *Endocrinology* 26: 54. 1940.
KORENCHEVSKY, V.: *Brit. M. J.* 2: 896. 1937.
KORENCHEVSKY, V., M. DENNISON AND S. SIMPSON: *Biochem. J.* 29: 2534. 1935.
KURZROK, L., C. H. BIRNBERG, AND S. LIVINGSTON: *Endocrinology* 22: 243. 1938.
KURZROK, L., C. H. BIRNBERG, AND S. LIVINGSTON: *Endocrinology* 24: 347. 1939.
KURZROK, R., AND P. O'CONNELL: *Endocrinology*, 23: 476. 1938.
LACKNER, J., L. KROHN, AND S. SOSKIN: *Am. J. Obst. & Gynec.* 34: 248. 1937.
LAROCHE, G., H. SIMONNET, AND BOMPARD, E.: *Compt. Rend. Soc. de Biol.* 129: 953. 1938.
LEONARD, L., V. SAGER, AND J. HAMILTON: *Proc. Soc. Exper. Biol. & Med.* 37: 362. 1937.
LIPSCHUTZ, A., L. VARGUS, AND O. RUIZ: *Lancet* 237: 867. 1939.
LOESER, A. A.: *Lancet* 1: 373. 1938.
MAZER, M., AND C. MAZER: *Endocrinology* 24: 175. 1935.
MIESCHER, K., E. WETTSTEIN, AND E. TSCHOPP: *Biochem. J.* 30: 1970. 1936.
NATHANSON, I., AND L. TOWNE: *Endocrinology* 25: 754. 1939.
NELSON, W. O., AND T. GALLAGHER: *Science* 84: 230. 1936.
NELSON, W. O., AND C. MERCKEL: *Proc. Soc. Exper. Biol. & Med.* 36: 231. 1937.
PAPANICOLAOU, G. N., H. RIPLEY, AND E. SCHORR: *Endocrinology* 24: 339. 1939.
PARKES, A. S.: *Lancet* 2: 674. 1936.
ROBSON, J.: *Proc. Soc. Exper. Biol. & Med.* 35: 49. 1936.
ROBSON, J.: *Quart. J. Exper. Physiol.* 6: 355. 1937.
ROBSON, J.: *Proc. Soc. Exper. Biol. & Med.* 34: 301. 1936.
ROTHERMICH, N.: *Endocrinolgoy* 25: 520. 1939.
RUBENSTEIN, H., AND A. ABARBANEL: *Am. J. Obst. & Gynec.* 37: 309. 1939.
RUZICKA, L., AND A. WETTSTEIN: *Helv. Clin. Acta.* 18: 1264. 1935.
SALMON, U. J.: *Proc. Soc. Exper. Biol. & Med.* 37: 488. 1937.
SALMON, U. J.: *Proc. Soc. Exper. Biol. & Med.* 38: 352. 1938.
SALMON, U. J.: *Endocrinology* 23: 779. 1938.
SALMON, U. J., R. I. WALTER, AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 39: 467. 1938.
SALMON, U. J., S. H. GEIST, AND R. I. WALTER: *Am. J. Obst. & Gynec.* 38: 264. 1939.
SEIGLER, S., AND L. SILVERSTEIN: *Am. J. Obst. & Gynec.* 39: 109. 1940.
SELYE, H., J. S. L. BROWNE, AND K. COLLIP: *Proc. Soc. Exper. Biol. & Med.* 34: 472. 1936.
SELYE, H., C. MCEUEN, AND J. COLLIP: *Proc. Soc. Exper. Biol. & Med.* 34: 30. 1936.
SHORR, E., G. PAPANICOLAOU, AND B. STIMMEL: *Proc. Soc. Exper. Biol. & Med.* 38: 759. 1938.
SPENCE, A. W.: *Lancet* 237: 820. 1939.
STURGIS, W. C., A. ABARBANEL, AND S. NADER: *Am. J. Obst. & Gynec.* 39: 102. 1940.
WOLFE, J. M., AND J. B. HAMILTON: *Endocrinology* 31: 603. 1937
ZONDEK, B.: *Nature* 33: 209, 494. 1934.
ZUCKERMAN, S.: *Lancet* 2: 676. 1937.

DISCUSSION

RATIONALE FOR ANDROGEN THERAPY IN GYNECOLOGY

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DURING THE PAST three years, many reports have appeared on the therapeutic properties of a synthetic male hormone (testosterone) in the treatment of a variety of functional gynecological conditions, the menopause (1–5), functional bleeding (6–17) dysmenorrhea (18, 19), mastopathies (6, 20, 21), lactation (22, 23) and pre-menstrual tension (18, 24). A survey of the literature reveals that the studies on the use of this hormone in women are almost entirely clinical in character. It must be confessed that the experience of the past few years has engendered considerable skepticism about the value of purely clinical reports when dealing with the evaluation of a new endocrine therapeutic agent. One need but review the literature of the past 6 or 7 years and recall the glowing reports describing the brilliant therapeutic results attributed to chorionic gonadotropic hormone, pituitary extracts, corpus luteum substances, estrogens, etc., in doses which subsequently were shown to be inadequate for any physiologic effect, to put us on our guard. Unfortunately, at present, the accurate appraisal of an endocrine therapeutic agent is complicated by the paucity of objective criteria and by the difficulty of evaluating the role played by psychic factors both in the etiology and in the therapeutic results achieved. For these reasons, in our investigations of the therapeutic efficacy of various endocrine substances, our group of workers at the Mount Sinai Hospital have employed, wherever feasible, objective methods of study in correlation with observations of the subjective reactions of the patients. We are aware that the methods of study available at present are neither sufficiently sensitive nor wide enough in scope to reveal the slight abnormalities of endocrine function and probably detect only the gross deviations from the normal. Nevertheless, the employment of objective criteria of biologic effectiveness, paralleled with clinical observations, should lead to a more realistic appraisal of the role played by the administered hormone and, furthermore, should tend to eliminate wishful thinking from the field of endocrine therapy.

This discussion presents, briefly (I) a review of the animal experimental work, (II) the results of our experimental studies of the somatic effects of androgens administered to women, and (III) the correlation of these phenomena with certain therapeutic effects and a discussion of the theoretical implications arising from these studies.

I. BIOLOGIC EFFECTS OF ANDROGENS ADMINISTERED TO FEMALE ANIMALS

It is not within the scope of this discussion to submit the animal experimental work to detailed analysis, but a survey of the literature reveals certain striking and, what appear to be, contradictory findings.

Action of Androgens on the Uterus and Vagina

Anti-estrogen action. The reports of a number of investigators seem to indicate that androgens counteract or negate the biologic effects of estrogens. In this group belong the reports of those investigators who have noted suppression of the estrus smear reaction in rats and mice following the administration of testicular extracts (25), androsterone (26), androstanediol (27), androstenedione (27), testosterone (27, 28, 29) and testosterone propionate (26, 33–43), and suppression of uterine (30, 31), and fallopian tube motility (32). These experiments would seem to indicate that androgens, when administered to females, act as antagonists of the estrogens, counteracting their physiologic action. Because of the obvious therapeutic implications arising from these studies, this aspect of the animal experimental work has been utilized as a basis for the clinical use of androgens in women. There is a fallacy, however, in the application of these observations to problems of gynecologic therapy which will be discussed later.

Gynecogenic (estromimetic and progestomimetic) action. Further study of the literature reveals that this group of investigations represents only one phase of androgen action in females, since other workers have shown that when certain of the androgens are administered to female animals, the hormones actually have a stimulating effect on the genital tract, simulating (estromimetic), augmenting or, like progesterone (progestomimetic), complementing the action of the estrogens. This is shown by the following observations.

Estromimetic action. Androsterone (44, 45), transdehydroandrosterone (46, 47), androstanediol (46, 49, 50, 51), androstenedione (48, 50, 52, 53, 54), testosterone (42, 47) and testosterone propionate (47, 54, 57) cause hypertophy of all the layers of the uterus and vagina (metrotrophic and

colpotrophic action) of intact and ovariectomized mature rats and guinea pigs. Furthermore, when any one of these hormones (with the exception of transdehydroandrosterone) is administered simultaneously with estrone, the estrone effect on the weight and histologic structure of the uterus and vagina is augmented (42, 47, 56). In immature rats, androstenedione (58), androstenediol (50, 52, 59, 60), testosterone (48, 58) and testosterone propionate (59, 60, 61) cause precocious opening of the vagina and hypertrophy of the uterus and vagina. The same effects are produced by testosterone propionate in ovariectomized immatures (60, 62, 63, 64).

Progestomimetic action. It has also been shown that testosterone propionate produces progestational changes in the endometrium of ovariectomized rats (47, 65) and cats (66); that testosterone has a similar action in estrogen-primed immature rabbits (67) and in estrogen-primed spayed adult rabbits (68).

Action of Androgens on the Ovaries

Inhibitory. A number of investigators have reported that androgens have an inhibitory effect on the activity of the ovaries. The first reported observation of this phenomenon is probably that of Neumann (69) who induced sterility in mice treated with large doses of testicular tissue. Groher (70) subsequently reported ovarian atrophy in mice treated with testicular extract. Castelnuovo (71) and Regnier (72, 73) have described atrophy of the ovaries of fish treated with a testicular extract and testosterone propionate. Kobayashi (74) (using testis emulsion), Schoeller and Gehrke (75) (using androsterone benzoate) and Ludwig and Von Ries (76) (using testosterone propionate) inhibited ovulation in fowls. Traina-Rao and de Palo (77) obtained follicular atresia in guinea pigs with testosterone propionate. Zuckerman (78) reported inhibition of follicular growth and luteinization in *Macacca mulatta* with testosterone propionate. McEuen, Selye and Collip (37) reported inhibition of the normal ovarian growth-increment of immature rats injected daily with 2 mg. of testosterone propionate for 22 days. In rabbits, Cotte, Martin and Mankiewicz (79) reported follicular atresia in rabbits following treatment with testosterone propionate. Mazer and Mazer (80) have described inhibition of follicle development and atrophy of the ovaries of immature and adult rats, following prolonged treatment with testosterone propionate. Following the discontinuation of the testosterone injections, normal ovarian cyclical changes reappeared. In guinea pigs, Boling and Hamilton (81) have reported that testosterone propionate suppresses follicle growth and ovulation during a 6 to 18-day period of injection. In adult female mice Selye (82) has found that daily administration of 5 mg. of testosterone propionate for 20 days causes decrease in the total size of the ovaries, disappearance of normal corpora lutea and marked follicle stimulation with the formation of follicle and, occasionally, corpora lutea cysts.

Gonadotropic action. In contrast to the observations described above, other investigators have reported findings which appear to indicate that androgens have a gonadotropic action. Migliavacca (83, 84, 85) has described induction of follicular growth in the ovaries of guinea pigs with small doses of testicular extracts and ovarian atrophy with large doses. Shapiro and Zwarenstein (86) have reported the induction of ovulation in the *Xenopus laevis* with methyl testosterone. In immature rats, Hohlweg (61) has obtained precocious luteinization with dehydroandrosterone and, inconstantly, with testosterone and no effect with androsterone. Wolfe and Hamilton (39) reported an increase in the size of the corpora lutea of adult rats treated with 15 mg. of testosterone propionate daily for 10 days. Gonadotropic effects (manifested by follicle stimulation and corpora lutea) in immature rats have been induced with androstenediol and testosterone propionate (59, 60, 89) and attributed to pituitary stimulation. These findings were confirmed (62, 63). In immature mice ovaries, Starkey and Leathem (87) found that testosterone propionate stimulated follicle growth but no corpora lutea formation. Freed, Greenhill and Soskin (88) have reported that in adult rats, receiving 0.05 mg. of testosterone propionate daily for 16 days, the ovaries reveal inhibition of follicle development, whereas rats receiving 1.0 mg. per day show numerous large corpora lutea. That the gonadotropic effect produced by testosterone propionate is mediated through the pituitary was shown by Nathanson, Franseen and Sweeney (63) and Leathem and Starkey (64), who found that testosterone propionate had no gonadotropic effect in hypophysectomized rats and mice.

Action of Androgens on the Hypophysis

The effects of androgen administration upon the hypophysis of experimental animals are difficult to evaluate because of the variety of criteria used by different investigators, viz., the effect of androgen administration upon: *a*), changes in pituitary weight (42, 45, 54, 90, 91); *b*), estrogen-induced hyperplasia (92); *c*), gonadotropic potency, measured by subsequent implantation studies (93–96); *d*), cytological changes (39, 97–100); and *e*), parabiotic animals (101, 102, 103).

Pituitary weights. Androsterone, androstanediol (42, 45, 54), testosterone, testosterone acetate and testosterone propionate (90, 91) appear to cause a slight decrease in the hypophysis weight of some adult rats. Bottomley and Folley (104) found no changes in weight of the hypophyses of young male guinea pigs treated with a variety of androgens. MeEuen, Selye and Collip (37) observed no gross changes in the pituitary of rats after prolonged testosterone injections.

Estrogen-induced hyperplasia. Wolfe and Hamilton (90, 91) were able to suppress the small but definite increase in hypophysis weight, induced by large amounts of estrone, by simultaneous injection of testosterone acetate. The hypertrophy of the hypophysis caused by large doses of estrogens, administered for long periods of time (97, 105–109), can be partially suppressed by the administration of androsterone, dehydroandrosterone and testosterone propionate (92).

Implantation experiments. That the gonadotropic activity of the hypophysis is considerably augmented following castration has been shown by the implantation of these castration hypophyses into immature animals (93–96). The gonadotropic potency of these implants is decreased if the castrated animals are injected with estrone (94, 97, 110,

111). Hamilton and Wolfe reported that a similar reduction of gonadotropic activity of the castration hypophysis can be accomplished with testosterone propionate (112). On the other hand, Bokslag and Vander Woerd (113, 114) found that testosterone propionate increases the gonadotropic activity of the hypophysis, while androsterone and testosterone had no definite effect.

Cytological changes in the hypophysis. The cytological changes resulting from ovariectomy can be reversed and prevented by the injection of androstanediol, androstenedione and androsterone (51). Wolfe and Hamilton (39, 90, 91, 97, 98, 115) induced degranulation of the basophils (but no significant changes in the acidophils or chromophobes) with daily injections of 0.5 mg. of testosterone propionate for 10 days. On the other hand, injection of 2 mg. per day for 10 days caused degranulation of the chromophil cells and enlargement of the negative images of the Golgi apparatus. Schoeller, Dohrn and Hohlweg (116) prevented, for 15 days after gonadectomy, the changes in the hypophysis of both male and female by the administration of estradiol benzoate, testosterone, testosterone propionate and androsterone. The hypophyses of rats treated with large doses of estrone show marked degranulation of the chromophils and increase in the size and number of the chromophobes. Wolfe and Hamilton were able to partially suppress this effect by administration of androgens simultaneously with the estrone (90, 91).

Parabiosis experiments. By the use of parabiotic rats, Hertz and Meyer (101) and Cutuly and Cutuly (102, 103) have demonstrated an inhibitory effect of androgens on the gonadotropic activity of the hypophysis.

As one surveys the results of the numerous experimental studies, it seems that, in intact immature and adult rats, small doses of testosterone propionate, administered for a short period, have a stimulating effect upon the hypophysis, inducing the secretion of gonadotropic hormone, whereas prolonged administration of the same hormone results in suppression of gonadotropic hormone activity. In gonadectomized animals, androgen administration appears to have an inhibitory effect upon the hyperactive hypophysis.

Action of Androgens on the Breast

Androstanediol (51) androstenedione (35), testosterone (117, 118) and testosterone propionate (38, 57, 117–119) cause hypertrophy of the mammary glands in female rats and of the nipples of male and female guinea pigs (120, 121). Nelson and Merckel (35) found that androsterone had no effect on the mammary glands of rats, while Jadassohn and his coworkers (120) were able to produce hypertrophy of the nipples in male guinea pigs by local application of androsterone in watery solution.

Geschickter and Astwood (122) reported mammary alveolar growth following testosterone propionate administration in rhesus monkeys, while Folley, Guthkelch and Zuckerman (123) reported papillomatous changes in the mammary duct epithelium in some species after testosterone administration. Van Wagenen, and Folley (124) found that in pre-adolescent ovariectomized rhesus monkeys, testosterone propionate stimulates a secretory condition in the mammary gland epithelium, leading to dilatation of the new alveoli. Δ^5trans-dehydroisonandrosterone and Δ^5trans-androstenediol produced similar but less marked effects. Cis-androsterone produced only a very slight reaction.

Arrhenomimetic Effects

The writer has felt the need for a term to designate the phenomenon of male secondary sex characteristics induced in females by androgens. "Andromimetic" has come to denote simulation of the action of androgens which, in females, includes estromimetic and progestomimetic, as well as the virilization effects. To specifically designate the latter phase of androgen activity in females, the writer suggests the term "arrhenomimetic."

Antenatal administration of androgens. The first experiments on this subject were performed by Dantchakoff (125) who injected testosterone propionate into hens' eggs and studied the subsequent changes in the gonads and behavior of the chicks. He reported that the female chicks developed hypertrophy of the combs and male behavior, but no changes in their plumage. Further studies followed: on rats (126–129); on mice (130); and on cats (66). These workers injected the pregnant females with androgens and studied the effect on the offspring. In their essentials, the results of these investigators are similar—mammalian intersexuality being produced.

Postnatal administration of androgens. Enlargement of the clitoris to penis-like structures has been produced with testicular grafts (131–136); with male urine extracts (47, 137–143). Zuckerman (78) has found that testosterone propionate is most potent in this regard, and Δ^5androstenediol least potent. Testosterone and Δ^5androstenedione have intermediate degrees of activity.

The small peri-urethral glands have been identified as the homologues of the prostate (144–148). Androstanediol, androstenedione, testosterone, testosterone propionate and androsterone cause hypertorphy of these glands in immature and mature, normal and ovariectomized rats (46, 56, 59, 60, 146, 147, 149). Dehydroandrosterone produces only slight enlargement.

Dantchakoff had noted that injection of testosterone propionate into eggs made the female chicks subsequently manifest male behavior characteristics (crowing and fighting). Allee and Collias (150) reported crowing in hens and Leonard (151), Shoemaker (152) and Baldwin, Goldin and Metfessel (153) singing in female roller canaries as a result of testosterone propionate administration.

Summary of Animal Experimental Studies

A survey of the experimental literature reveals the protean character of the biologic properties of androgens. It is very difficult to correlate the varied and, at times, contradictory experimental results. However, from the maze of paradoxical phenomena induced by androgens, one can discern three outstanding biological properties.

1. Gynecomimetic Action
   (*a*) Estromimetic (simulating the action of estrogens
   (*b*) Progestomimetic (simulating the action of progesterone)
   (*c*) Gonadotropic (mediated through the hypophysis)
   (*d*) Hypophyseotropic (stimulating the gonadotropic activity of the hypophysis)
   (*e*) Mammotropic (stimulating growth of the breasts)
2. Anti-Gynecogenic Action (opposing the feminization factors)
   (*a*) Suppression of the normal estrus (cornification) reaction in the vagina
   (*b*) Nullification of some of the biologic action of administered estrogens (on vagina, pituitary)
   (*c*) Suppression of ovulation and follicle growth, through inhibition of the gonadotropic activity of the pituitary.
3. Arrhenomimetic Action (simulating the male secondary sex characteristics)
   (*a*) Hypertrophy of the clitoris and preputial glands
   (*b*) Growth of combs in female chicks
   (*c*) Crowing in hens
   (*d*) Singing in female canaries
   (*e*) Male behavior

It seems that some of the androgens exhibit properties which appear to be (in a biological sense) antithetical to each other. Thus testosterone propionate can simultaneously induce in the same animal, both gynecogenic and arrhenomimetic effects. This is well illustrated by the simple experiment of administering 5 mg. of testosterone propionate to an immature female rat (60). Within 4 days the vagina opens, the vaginal mucosa reveals an estrus reaction, the uterus is hypertrophied and the ovaries show growing follicles and corpora lutea (gynecogenic effects); at the same time, the clitoris and preputial glands are hypertrophied (arrhenomimetic effects).

Realization of the biphasic character of the biologic properties of androgens will serve to clarify a number of what may seem to be irreconcilable observations. It should be borne in mind, furthermore, that although the androgens manifest bisexual potency in females, under appropriate experimental conditions, one or the other component effect is dominant. Which of these two effects dominates the biologic picture is determined by a number of factors, viz.: the chemical constitution of the androgen; the dose of the hormone administered and the duration of treatment; the species, age and endocrine status of the animal.

It is obvious, from the experimental studies in animals, that we must abandon the concept of a simple androgen-estrogen antagonism. The use of androgens therapeutically in women was based upon their estrus suppressing action which was interpreted as indicating nullification of the biologic action of estrogens. This concept of a nullifying action is true with regard to cornification of the vaginal mucosa, but histologic examination of the vaginae of these animals reveals that the disappearance of the cornified cells from the smear is not, as one might expect, the result of regressive changes (such as one would find as a result of estrogen deprivation produced by castration or old age) but, as Korenchevsky (154) and his coworkers have pointed out, due to *mucinification* of the mucosa, such as one sees in pregnancy. The muscular layers of the vagina, at the same time, show evidence of increased growth and the uteri of these animals show no signs of estrogen inactivation but are actually hypertrophied and frequently present striking progestational changes in the endometrium. The concept of estrogen-androgen antagonism in animals is based upon only one phase of androgen-estrogen inter-relations and ignores the gynecogenic properties of androgens, which actually simulate, complement or augment the action of the estrogens.

In view of the paradoxical character of the effects of androgen administration to female animals, it is hardly logical to attempt to apply the result of the experimental studies in animals to the human female. Realization of this, prompted our group of workers, several years ago, to undertake a series of experiments to determine the biologic effects of androgens in the human female.

II. BIOLOGIC EFFECTS OF ANDROGENS IN THE HUMAN FEMALE

Material and Methods

These studies were performed on a series of women with regular menstrual cycles, as well as on ovariectomized and post-menopausal women. In the regularly menstruating women, the effect of varied doses of androgens was studied upon: *a*), menstrual function; *b*), the endometrial pattern; *c*), the vaginal smears; *d*), the histologic structure of the vaginal mucosa; *e*), the gonadotropic activity of the hypophysis (by gonadotropin excretion studies); *f*), ovulation (histologic study of the ovaries); g), progesterone production (by excretion of pregnandiol glucuronidate); *h*), fallopian tube peristalsis and uterine contractions; and *i*), constitutional effects.

In ovariectomized and post-menopausal women, the effect of testosterone propionate was studied upon: *a*), gonadotropic activity of the hypophysis (by gonadotropin excretion); *b*), vaginal mucosa (smears and histologic pattern; and *c*), the endometrial pattern.

The following androgens were used: testosterone, testosterone propionate, methyl testosterone, ethinyl testosterone, androsterone, androstenediol and androstenedione.

The methods of administration were: *a*), intramuscular and subcutaneous injection in solution in sesame oil (testosterone propionate, androsterone, androstenediol (and androstenedione); *b*), subcutaneous implantation (testosterone and testosterone propionate); *c*), orally ethinyl testosterone, methyl testosterone and testosterone); *d*), sublingual (testosterone in propylene glycol); and *e*), cutaneous inunction (testosterone and methyl testosterone).

Although the majority of these studies have been reported (3, 8, 18, 155–159), their close relationship to the factors involved in a number of functional gynecologic conditions that are being treated with androgens make it worthwhile to present these observations in a coordinated form here.

The major part of our studies, which included a group of 362 cases, was performed with testosterone propionate. During 1936, before testosterone propionate became available, we used androsterone, dehydroandrosterone benzoate and testosterone. Our preliminary studies with these solutions, probably because of the small doses used (5 to 20 mg. per week), yielded results which were equivocal. Because of the demonstrated superlative potency of testosterone propionate (160) and its widespread clinical use, the biological properties of this compound will be presented in detail.

Biologic Effects of Testosterone Propionate in the Human Cyclical Female

The biologic effects produced by testosterone propionate are conditioned by the dosage and the phase of the cycle during which the hormone is administered.

Effect of different doses. If 500 mg. or more of testosterone propionate are given intramuscularly or subcutaneously in divided doses throughout one cycle, to a woman with a regular menstrual cycle, the following effects are noted.

(*a*) The next menstrual period is suppressed or delayed by 2 or more weeks.

(*b*) The endometrium, at the end of about 4 weeks, is found to show absence of the secretory pattern, hypoplasia or atrophy.

(*c*) The vaginal smear presents a picture characteristic of an estrogen deficiency (disappearance of the cornified squamous epithelial cells and their replacement by the small atrophy cells and leucocytes).

(*d*) The vaginal mucosa shows involutional changes similar to post-menopause atrophy. At the same time, the glycogen in the desquamated vaginal epithelial cells is strikingly reduced or disappears completely.

(*e*) The normal contractions of the fallopian tubes and uterus are suppressed.

Usually within 3 to 5 weeks after discontinuation of the testosterone propionate, the normal proliferative (estrogen) phenomena reappear in the endometrium and vaginal mucosa, leading to restoration of normal endometrial and vaginal patterns and a regular menstrual cycle.

When 200 to 300 mg. of the hormone are administered during one cycle, menstruation is not suppressed but the amount of bleeding is usually diminished. In some patients this amount of hormone causes menstruation to occur 3 to 6 days early and appreciably increases the flow for several days.

Time of administration. It was noted that if 500 to 1000 mg. of testosterone propionate are given during the first 10 to 12 days of the cycle, menstruation may be delayed for 1 to 4 weeks, accompanied by regressive changes in the endometrium and vaginal mucous membrane. Similar amounts, administered during the last 10 to 14 days of the cycle had no perceptible effect on the menstrual period, the endometrium or the vaginal smears during the current cycle. These observations were interpreted as indicating that, if given early in the cycle, the hormone inhibits the secretion of gonadotropic hormone by the hypophysis, which results in suppression of estrogen and progesterone production, whereas, if given in the latter part of the cycle, after the gonadotropic hormone has exerted its action and ovulation has occurred, the production of estrogen and progesterone during the current cycle is not interrupted and these substances exert their physiologic action on the endometrium.

Gonadotropic activity of the hypophysis. Gonadotropic hormone studies performed on 3 cyclical women who were given inhibiting doses of testosterone propionate during the first 2 weeks of the cycle, showed an absence of gonadotropic hormone excretion during the current cycle. These women revealed characteristic morphologic regression in the endometrium and vagina associated with suppression of the current menses. The conclusion was drawn from these studies that inhibition of the gonadotropic hormone secretion by the hypophysis had resulted from the administration of testosterone propionate.

Ovulation. The failure of the progestational pattern to appear in the endometrium after testosterone propionate administration was interpreted as indicating inhibition of ovulation. In order to determine this point conclusively, a number of patients with regular ovulatory cycles (determined by the finding of characteristic progestational endometria during the premenstrual period) were given 600 to 1000 mg. of testosterone propionate during one cycle (159). These patients were then operated on (for uterine fibroids) and histologic studies of the ovaries, endometrium and vagina were made. No evidence of recent ovulation or corpora lutea was found. The endometrium and vaginal mucosa revealed hypoplasia or atrophy, indicative of estrogen deficiency. These findings confirm earlier studies of the endometrium which indi-

cated that testosterone propionate inhibits ovulation and estrogen and progesterone production.

Progesterone production (as determined by pregnandiol excretion). In 4 cases of the same series, pregnandiol excretion studies were performed during the period of androgen administration. It was found that if testosterone propionate is given in adequate amounts (over 600 mg.) during the first 7 to 10 days of the cycle, no pregnandiol appears in the urine; during the current cycle menstruation does not occur; the endometrium and vaginal mucosa are reduced to a state of hypoplasia; and the ovaries show no recent corpus luteum. In 2 cases in which testosterone injections were begun after the 14th day of the cycle, normal pregnandiol excretion was found.

Fallopian tube peristalsis and uterine contractility. Doses of testosterone propionate that are sufficient to suppress menstruation also suppress the normal tubal contractions (157) and modify (161) uterine contractions.

Estrogen deficiency phenomena. A number of the patients receiving doses of more than 500 mg. complained of pruritus vulvae and vaginal discomfort. Examination revealed that these patients had developed a vaginitis similar in appearance to the senile type. In 2 cases this was complicated by a trichomonas infection. The vaginitis cleared up spontaneously in all within 2 to 3 weeks.

Some of the women in the fifth decade complained of flushes which developed during the period of amenorrhea. This is probably attributable to an estrogen deficiency. These lasted only for about 2 weeks, their disappearance coinciding with the return of the normal estrogenic type of vaginal smear.

Constitutional Effects

Arrhenomimetic phenomena. Some interesting endocrinologic effects of androgen administration have been reported by several observers (6, 8, 18, 158, 163). These are hypertrichosis, hoarseness and enlargement of the clitoris. In a series of 362 cases treated by our group with doses varying from 100 to 3200 mg., the hypertrichosis was present in 6%, voice changes in 7.7% and acne in 4.4%.

Hypertrichosis and hoarseness. It should be pointed out that these arrhenomimetic phenomena appear to be conditioned by the dosage administered and usually occur only if large doses of the hormone (500 mg. or more per month) are given. Thus, in the entire series of 362 cases, in only 4 was hirsuties noted with doses of less than 500 mg. The hirsuties was slight in degree and both of these had had slight hypertrichosis before the testosterone propionate was administered. In only 3 cases was hoarseness produced with doses of less than 500 mg. (470, 315, and 425 mg.). The hypertrichosis and voice changes that developed in the series of cases treated with 600 mg. or less were all comparatively slight in degree and began to regress after the discontinuation of the injections. The tempo of regression varied somewhat, but in the majority of this series, the arrhenomimetic phenomena disappeared within 3 to 6 months after the cessation of the androgen therapy. In none of the cases of this series was either hypertrichosis or hoarseness a serious problem. In many instances the patients were not aware of anything unusual until their attention was directed to a slight hoarseness or to hypertrichosis on the lip or chin.

In several experimental cases, treated during the early stages of our investigations with huge doses of testosterone propionate (approximately 2000 mg.), the hypertrichosis and voice changes were very marked and persisted for as long as 14 months after the cessation of treatment.

Acne. Some of the patients treated with testosterone propionate developed a scattering of acneiform papules on the back, chest and face at the end of about 2 weeks of treatment. The acne did not appear to be directly dependent upon the amount of hormone administered. Thus some of the patients receiving the largest doses (upwards of 1500 mg.) had no acne, whereas, some cases developed some acne after as little as 150 mg. These patients have invariably been found to have had an acne at some time before the androgen treatment. The acne in this group has proven to be more persistent than in those who had no antecedent history of acne.

Clitoris enlargement. A slight hypertrophy of the clitoris was noted in only 6 patients all of whom received from 2160 to 2400 mg. of testosterone propionate. In the majority of the patients receiving 500 mg. or more per month, the clitoris (and surrounding tissues) appeared to become congested and hypersensitive.

Libido. A number of the patients volunteered the information that they experienced definite increase in libido during the course of injections and for several weeks thereafter. In many of these patients, the clitoris was erythematous and very sensitive to touch. The majority of these cases received more than 500 mg. of the hormone in one month.

Evaluation of this effect is, for obvious reasons, beset with difficulties. I am convinced that it is a specific pharmacologic effect and not merely a concomitant of the amelioration of the clinical condition (e.g., the menorrhagia, dysmenorrhea, etc.). My attention was first drawn to it by several elderly women who found the resurgence of libido distressing. The phenomenon is equally as striking among young women. A number of married women, who had considered themselves

frigid, stated that after receiving the testosterone propionate injections they experienced a marked increase in coital gratification, culminating in an orgasm. In the majority of these cases, the effects wore off within several weeks after the discontinuation of the injections. In a small number, the improvement continued for varying periods after discontinuation of treatment. (The longest post-therapy effect has, up to the present writing, been 32 months.)

General reactions. It is noteworthy that patients receiving between 100 and 300 mg. during the course of one month reported an increased feeling of well-being. They stated that they did not fatigue as easily and had improved appetite. It is obviously difficult to properly evaluate these declarations. They may be entirely attributable to incidental psychotherapeutic reactions. However, it is worthy of note that, associated with these subjective symptoms, the patients experienced an increase in weight varying from 3 to 12 pounds during the course of 4 to 6 weeks. In a number of instances, the patients developed slight edema of the hands and ankles. Animal studies by Thorne and his coworkers (164–166) on the water and salt-retaining properties of the sex hormones suggest that the weight gain in these women may be partly due to water retention. The studies of Kenyon et al. (167) on eunuchs have revealed that following treatment with testosterone propionate the patients experienced weight gains associated with nitrogen and sodium retention and a slight increase in basal metabolic rate. The authors attribute the nitrogen retention to protein storage which may contribute to the weight gain. McCullagh and McGurl (168) reported sodium and chloride retention (but no significant change in nitrogen excretion) associated with gain in weight in an elderly man following treatment with testosterone propionate.

Action of Testosterone Propionate in Menopausal and Ovariectomized Women

Hypophysis, vaginal mucosa and endometrium. In 1937, the author studied the effect of testosterone propionate on gonadotropic hormone excretion, vaginal smear reaction and symptoms of a human female castrate (3) and reported that following treatment with testosterone propionate the patient experienced relief of her symptoms and, at the same time, the gonadotropic hormone disappeared from the urine and the vaginal smears revealed estrogenic effects. Shorr, Papanicolaou and Stimmel (169) and Nathanson and Towne (170) confirmed the pituitary inhibiting action of testosterone but the former and Rothermich (171) were not able to demonstrate the estromimetic effect on the menopausal vaginal smears. On the other hand, Nathanson and Towne reported estromimetic effects in the vaginal smears and increased urinary excretion of estrogens in female castrates treated with testosterone propionate.

Estromimetic action of testosterone propionate. We have amplified our initial studies of post-menopause and castrate patients, during the past 3½ years, and have found that the vaginal smear effects varied with the dose of testosterone propionate administered. In 8 out of 43 cases, the smears changed from the typical 'negative' (estrogen deficiency) to the characteristic estrogen type. With one exception, this effect on the smear was noted only when concentrated courses (50 to 100 mg. per day) of testosterone propionate were administered for periods of at least 3 weeks. In smaller doses (10 to 25 mg., 2 or 3 times weekly or daily), testosterone propionate does not produce this estromimetic action, even if continued for many months. Thus, several cases had been given total doses ranging up to 2800 mg., during periods of 4 to 9 months, without producing estromimetic effects in the smears. The exception mentioned above was a patient who began to show estromimetic effects in the vaginal smears after 465 mg. of testosterone propionate, given in 27 days (3). When the experiment was repeated in the same patient, several months later (after her smear had regressed to the pre-treatment status) similar effects were not elicited until the patient had received a total of 1250 mg. over a period of 18 days.

Believing that the discrepancy in these reports might possibly be due to individual variations in the interpretations of vaginal smears, we have studied histologic (biopsy) sections of the vaginal mucous membrane in a series of menopausal and castrated women, before and after treatment with testosterone propionate, and have found unequivocal evidence that concentrated courses of testosterone propionate stimulate proliferation of the epithelial elements of the atrophic (estrogen deficient) vaginal mucosa. It should be borne in mind that this estromimetic effect can only be produced with huge doses administered in concentrated form. The failure of Shorr, Papanicolaou and Stimmel (169) and Rothermich (171) to find estromimetic effects in their cases is probably attributable to inadequate dosage. It is noteworthy that testosterone propionate appears to have no estromimetic effect on the atrophic uterine mucosa, the endometrial biopsies revealing no evidence of proliferation even in cases receiving the concentrated doses. Testosterone propionate has also been shown to have no progestomimetic effect on the estrogen-primed endometrium (162).

Methyl Testosterone

In an attempt to obviate the necessity for intramuscular or subcutaneous injections, we had administered both testosterone and testosterone propionate by mouth, in doses varying from 100 to 550 mg., to 6

women, over periods varying from 4 to 10 weeks. In no case was any clinical or morphologic evidence of androgenic activity observed. We then investigated the activity of methyl testosterone administered by mouth. This compound was prepared from testosterone (172). Foss (173) reported its use in several cases of dysmenorrhea with varying results.

The study was conducted on a series of 46 cases. The dose varied from 15 to 100 mg. daily, over periods varying from 1 to 8 months. The total dosage varied from 500 to 4975 mg. Cyclical cases that were given 75 or 100 mg. daily, developed suppression of menstruation associated with striking involutional changes in the vaginal smears. This compound appears to be a very potent androgen when administered orally. Suppression of menstruation was accomplished with total doses varying from 1125 to 2200 mg. during one cycle. In our series, the minimal suppressive dose of testosterone propionate, administered parenterally, was 500 mg. Methyl testosterone appears to be approximately one-third to one-half as effective by mouth as testosterone propionate is parenterally. In the series of cases studied, hypertrichosis was distinctly less frequent than in patients treated with testosterone propionate. If this lower arrhenomimetic potency is confirmed in a larger series of cases, it would make methyl testosterone more valuable as a gynecologic therapeutic androgen than testosterone propionate. In every other aspect, methyl testosterone seems to act like testosterone propionate.

Pregneninolone

Biologic effects of ethinyl-testosterone (pregneninolone). This compound (174, 175) possesses a unique variety of biologic properties. In animals, it has a striking progestomimetic (176), some estromimetic (177, 178), and very slight andromimetic (177, 179) action. It is, furthermore, active when administered orally.

In a series of 20 cyclical women treated orally with doses varying from 30 to 60 mg., per day over periods of 1 to 2 months, none of the suppressive (anti-gynecogenic) effects, which were so strikingly produced by testosterone propionate and methyl testosterone, were observed (180). Menstruation was never suppressed and no estrogen deficiency phenomena appeared. Furthermore, in no instance did arrhenomimetic phenomena develop.

When pregneninolone was administered in doses of 60 mg. per day for several weeks to post-menopausal or castrated women with morphologic evidence of estrogen deficiency, the smears manifested estromimetic effects. The endometrium, however, failed to reveal any signs of proliferation. Smaller doses seemed to have no demonstrable effect on the vaginal smears (180).

When administered orally to post-menopausal women after adequate priming with estrogens, progestational changes were produced with doses of 300 to 600 mg., administered over periods of 1 to 2 weeks (181, 182).

No hirsuties, hoarseness or enlargement of the clitoris occurred in any of the patients.

Because of its low androgenic potency in animals, it was thought that pregneninolone might prove of value as a therapeutic agent, since the risk of arrhenomimetic effects would be minimal. Expectations, as regards the latter, were realized, but its low androgenic activity rendered it of limited value as a therapeutic androgen. In our experience, it has proved of value in some cases of dysmenorrhea, pre-menstrual tension and mastalgias, and of no value in the treatment of functional bleeding. Its chief potential value appears to lie in its progestomimetic property.

III. THEORETICAL CONSIDERATIONS

As one surveys the manifold endocrinologic ramifications of androgen action in women, one cannot but be impressed both with their physiological implications and therapeutic potentialities. Dr. Geist has reviewed and evaluated the clinical literature dealing with the use of testosterone propionate in the treatment of functional meno- and metrorrhagia, pre-menstrual tension, mastopathies and menopause syndrone. The high percentage of strikingly good clinical results obtained by independent observers in a variety of gynecologic disorders is sufficiently impressive to prompt us to seek an explanation for the therapeutic versatility of the androgens.

The therapeutic effectiveness of testosterone propionate appears to stem from the following properties: *a*), its ability to inhibit the gonadotropic activity of the hypophysis; *b*), to suppress or decrease estrogen production; *c*), to nullify or modify the activity of the gynecogens; *d*), to inhibit the proliferative processes in the endometrium; and *e*), to inhibit the reactivity of the uterine musculature.

Functional bleeding. In order to understand the mechanism of the therapeutic action of testosterone propionate in abnormal uterine bleeding, it is essential that we review our present knowledge of the physiological processes involved in normal menstruation. Here we can refer, only briefly, to those factors whose role with regard to menstruation has been definitely established. For accounts of the experimental studies and theories relating to menstruation, the reader is referred to several comprehensive reviews (183–188).

Role of hormonal factors in menstruation. It is generally accepted that uterine bleeding occurs whenever there is a withdrawal of the hormones controlling the growth phenomena of the endometrium, i.e.,

the estrogens and progesterone. But before menstruation actually occurs, a series of interesting vascular changes occur in the endometrium. The cyclical character of the vascular changes has been definitely established as a result of experimental studies (185, 186, 189–194). It is generally accepted that the superficial part of the stroma is supplied by a series of 'spiral arteries' (191) which arise from a plexus of blood vessels lying deep in the basalis, which in turn originate from parent vessels in the myometrium. Under the influence of progesterone, the spiral vessels in the superficial endometrium undergo rapid growth and become more strikingly coiled. After withdrawal of the growth stimulus to the endometrium, the superficial stroma loses water, the spiral arteries become compressed and stasis occurs. This is followed by leucocytic infiltration of the surrounding tissues. Local necrosis occurs and small hematomata develop which increase in size and rupture on the surface. This is followed by fragmentary desquamation of the endometrium and menstrual bleeding. This series of vascular events has been observed in ocular transplants of endometrium and, while histologic studies of the vascular elements of the endometrium in monkeys (189–191) and humans (192) tend to indicate that similar phenomena may occur in the human uterus, it should be remembered that, in situ, because of the altered physiological conditions, the process may be very different. As Reynolds (195) has pointed out, the uterus is a muscular organ which contracts vigorously during menstruation and these contractions undoubtedly influence the lymph flow and the amount of bleeding. Furthermore, the influence of the nerve supply to the uterus and its effect on these vascular phenomena has not as yet been thoroughly evaluated. So that, although the studies of Markee, Daron and others have added to our knowledge of the physiological processes involved in menstruation, they do not, at present, shed any light on the aspect of menstruation that is of paramount clinical interest, viz., the mechanism which controls the amount and duration of bleeding.

Hormonal causes of functional meno- and metrorrhagia. The majority of published clinical investigations, which had as their objective the determination of the cause or mechanism of abnormal uterine bleeding, were, unfortunately, confined to studies of the endometrial pattern and estrogen excretion. The morphologic studies have established, beyond question, the fact that excessive bleeding can occur from endometria showing proliferative, hyperplastic, secretory and even hypoplastic or atrophic patterns. It is significant that, with the exception of the comparatively uncommon cases of excessive bleeding associated with atrophic endometria, estrogen stimulation is essential in the development of each of these patterns. There is, furthermore, evidence in the excretion studies of Frank (196) of increased production of estrogens in patients with functional meno- and metrorrhagia.

Although there is considerable experimental evidence indicating that in women, as in monkeys, bleeding is initiated by withdrawal of estrogens and/or progesterone, there is no information available that explains the prolonged continuation of the bleeding and the excessive loss of blood which occurs in functional menorrhagia and meno-metrorrhagia. It seems to the writer, however, that the majority of cases of functional bleeding can be explained by excessive and abnormally prolonged stimulation by estrogens and/or progesterone. This view is based on the following observations. *a*), Endometrial biopsies obtained from patients with meno- or metrorrhagia, after bleeding for as long as 12 days, not infrequently reveal evidence of continued estrogen and/or progesterone stimulation, manifested by active proliferation of the epithelial elements and by various degrees of hyperplasia or composites of proliferation and secretory patterns. *b*), In menopausal women implanted with crystals of α-estradiol, in whom intense estrogenic stimulation is maintained for many weeks (and continued during the period of bleeding), we have observed evidence of active proliferation, even after 14 days of continuous, profuse bleeding. It is not unlikely, therefore, that functional meno-metrorrhagia may be caused by excessive and abnormally prolonged estrogen stimulation. It is, furthermore, not necessary to postulate estrogen withdrawal to explain the onset of bleeding, since bleeding can occur in spite of uninterrupted estrogen stimulation.

There is also some evidence which suggests that an aberration of progesterone action may be involved in the causation of some types of abnormal uterine bleeding. Thus Zondek and his coworkers (197, 198) have shown that progesterone can induce bleeding in cyclical women during the post-menstrual phase; Hamblen (199) has found abnormally high pregnandiol excretion in a patient with functional menorrhagia. Furthermore, we (162) have induced profuse bleeding lasting as long as 20 days, by the administration of large doses of progesterone (150 to 200 mg.) to menopausal women previously treated with doses of estrogens (10,000 R.U. estradiol benzoate, 3 times weekly, for 2 to 4 weeks), which usually caused no, or only brief, scanty bleeding.

Action of testosterone propionate in controlling functional menorrhagia. Starting with the assumption that excessive and abnormally prolonged stimulation by estrogens (and/or progesterone) is responsible for excessive uterine bleeding, it is not difficult (in view of the biologic properties of testosterone propionate in cyclical women) to understand how testosterone propionate is effective in controlling abnormal bleeding.

By suppressing the production of estrogens and progesterone at their source, by nullifying the growth promoting effects of these hormones upon the epithelial and vascular elements of the endometrium and by abolishing the pumping action of the uterine contractions, testosterone propionate (when administered in suppressive doses) causes complete involutional changes in the uterus, with consequent suppression of bleeding; or (in smaller doses) reduces the intensity of the stimulative action of the gynecogens on the vascular and myometrial tissues to the physiological level, with resultant normal uterine bleeding.

The extent to which the hypophysis is involved in this therapeutic effect is difficult to determine. That the gonadotropic activity of the hypophysis is inhibited by large doses of testosterone has been established, but whether gonadotropic function is affected by the small therapeutic doses that do not cause suppression of menstruation is, at present, unknown. It is conceivable that in therapeutic doses testosterone propionate reduces the gonadotropic activity of the hypophysis, with consequent reduction in the amounts of gynecogens produced by the ovaries. Furthermore, we have to explain the therapeutic effects obtained by doses of testosterone propionate that do not produce any detectable signs of morphologic regression in the endometrium. In answer, it can be pointed out that the effect of testosterone on the architecture of the endometrium is a gross manifestation and that therapeutic effects may be achieved through its inhibitory action on the vascular and muscular factors involved in menstruation without inducing demonstrable changes in the pattern of the endometrium.

Recently Abarbanel (200) has attributed the therapeutic effect of testosterone propionate to a 2-fold action on the uterine musculature causing "inhibition of the intermittent uterine contractions and a direct stimulative action upon the myometrial elements." The basis for the assumed stimulative action on the myometrium is the experimental studies of Korenchevsky et al. (47) who produced hypertrophy of the myometrium in rats with testosterone propionate. As has been pointed out above, testosterone produces effects in rats which are not reproducible in the human female. In the rat, testosterone has an estromimetic and progestomimetic action, producing proliferative and progestational changes in the endometrium as well as hypertrophy of the myometrium, whereas, in cyclical women, it is anti-gynecogenic, causing atrophy of the endometrium and suppression of the activity of the myometrium.

Functional dysmenorrhea. It does not fall within the province of this paper to discuss the various theories of the etiology of dysmenorrhea that have been advanced in recent years. These include purely mechanistic, psychogenic and hormonologic concepts. Recently, the tendency has been to favor the latter, attributing dysmenorrhea to a disturbance of the physiological estrogen-progesterone balance. Some writers have reported good therapeutic results with estrogens and others have been equally as enthusiastic about progesterone and chorionic gonadotropin.

The crux of the problem appears to lie in the fact that dysmenorrhea is not a clinico-pathological entity but rather a symptom complex which may be caused by a number of apparently unrelated factors, acting separately or in combination. In some cases, mechanical factors or intrauterine disease (adenomyosis), may be responsible for the symptoms. Furthermore, it is difficult to evaluate the role played by psychic factors both with regard to the causation of the symptoms and their amelioration. This probably accounts for the wide variety of therapeutic agents that have been found efficacious in the hands of different observers.

Hormonal factors in etiology of functional dysmenorrhea. There is undoubtedly a well-defined syndrome which occurs in patients in whom local organic disease and mechanical causes can be excluded with reasonable certainty. Although the literature is full of conflicting theories, there is considerable evidence which indicates that dysmenorrhea can be attributed to a disturbance of the normal rhythmic uterine contractions that occur during menstruation (201, 202). Because of the demonstrated inhibitory action of progesterone upon uterine contractions (203), it has been assumed, by a number of authors, that dysmenorrhea is caused by a progesterone deficiency. There is, however, very little factual evidence to support this theory. In a series of dysmenorrhea cases studied by us, we found typical pre-menstrual secretory endometria in all cases. Furthermore, in several patients in whom we found an absence of progestational changes in the endometrium pre-menstrually, the patients did not have dysmenorrhea. Another significant observation has been that in post-menopause cases in which uterine bleeding was induced with estrogens alone, the bleeding was accompanied by either very slight cramps or none at all; whereas, when some patients were subsequently given progesterone, in addition to estrogens, a number of them developed severe pain while bleeding. It is interesting, in this connection, that Hamblen (199) reported the excretion of abnormally large amounts of pregnandiol by a patient suffering from dysmenorrhea.

Testosterone propionate in dysmenorrhea. From all the evidence available, it seems that functional dysmenorrhea is caused by a disturbance in myometrial function which, in all probability, is the result of a lack of integration of the various hormonal factors that normally produce rhythmic painless contrac-

tions. Whether this is due to excessive estrogen and/or progesterone stimulation or to a disturbance of their physiological interrelations, is, at present, not clear. But as a basis for understanding the therapeutic action of testosterone, it is sufficient if we accept the hypothesis that it is some aberration of gynecogen action on the myometrium that is the cause of functional dysmenorrhea. It has been shown that testosterone completely suppresses the contractions of the fallopian tubes (32, 157) and uterus (30, 31). In smaller doses, its suppressive effect is less intense and it probably reduces the excessive and abnormal uterine contractions to physiologic patterns. Whether testosterone accomplishes this by depressing the reactivity of the myometrium or by modifying or reducing the stimulating action of the estrogens remains, for the present, unknown. To what extent the inhibitory action of testosterone propionate upon the gonadotropic activity of the hypophysis contributes to the therapeutic effect is, at this stage of our knowledge, a matter for conjecture.

Relation of therapeutic effect to endometrial pattern. During the early stages of our experimentation with the therapeutic properties of testosterone propionate, we administered suppressive doses to patients with dysmenorrhea, inducing advanced involutional changes in the uterus. Subsequently, normal cyclical bleeding recurred without dysmenorrhea. In a significant number of cases that have been observed for almost 3 years, without further treatment, the dysmenorrhea has not recurred. Endometrial biopsies performed after the resumption of menstruation revealed that the normal proliferative and secretory patterns were restored. If one were to judge from the endometrial patterns, it would seem that the estrogen-progesterone relationship which was established following the androgen therapy was identical with that which had prevailed before the administration of the testosterone propionate. There is, however, one significant clinical difference and that is the absence of dysmenorrhea. Obviously, whatever the nature of the readjustment may have been, it did not involve a disturbance of the normal cyclical processes in the ovaries nor a sufficient change in the estrogen-progesterone relations to lead to modification of the endometrial pattern. It is conceivable, as in the case of functional bleeding, that testosterone propionate may exert its therapeutic effect without necessarily creating repercussions that result in demonstrable changes in the architecture of the endometrium. This view is supported by the observation that fallopian tube peristalsis in women can be suppressed by doses of testosterone propionate that are insufficient to induce involutional changes in the endometrium (162), and also by the observation that ethinyl testosterone relieves some cases of dysmenorrhea although this compound does not, even in enormous doses, inhibit menstruation or induce involutional changes in the uterus.

How is one to account for the variable duration of the therapeutic effects after the discontinuation of the testosterone? Some cases remained symptom-free for the total period of observation which, in some instances, has been almost 3 years; in others, symptoms recurred with increasing intensity 1 or 2 months after the treatment was discontinued. In a number, repeated small courses of testosterone were required to keep the patients symptom-free. The latter type of response suggests that the basic disturbance may consist of a deficiency in a substance whose function it is to integrate or modify the action of the gynecogens and that testosterone propionate performs the same function. This, however, could hardly explain the prolonged therapeutic effect obtained in many cases unless we assume that the irritability of the myometrium is reduced by the testosterone propionate for a prolonged period or that the administration of testosterone propionate stimulates the production of physiologic androgens, presumably by the adrenal cortex.

The therapeutic action of testosterone in dysmenorrhea has been attributed to its progesterone-like action (204), this opinion being based on the progestomimetic action of testosterone in rats (47, 65) and rabbits (67,68). In view of the fact that a progesterone deficiency has never been demonstrated in functional dysmenorrhea and that testosterone has no progestomimetic action in humans, this view seems hardly tenable.

Pre-menstrual tension. This syndrome, first described by Frank (205), was attributed by him to an hyperestrinemia, associated with low estrogen excretion. In this syndrome, even more than in the case of dysmenorrhea, psychogenic factors appear to play an important, if ill-defined role. In spite of the fact that the syndrome consists of symptoms which are usually identified with neuroses and that one may find, in the patient's history, evidence suggesting a psychogenic etiology, it is important both as regards the therapy and prognosis to realize that the distressing symptoms are essentially expressions of an abnormal irritability of the autonomic nervous system and that the associated emotional disturbances are the result of an abnormal action of the gynecogens on the autonomic nervous system. Some of these patients undoubtedly would benefit from appropriate psychiatric care. In the writer's experience, however, the therapeutic results obtained with testosterone propionate alone (without any planned psycho-therapy) have been very satisfactory.

In attempting to determine the hormonic mecha-

nism that gives rise to premenstrual tension, the following observations must be taken into consideration:

(*a*) Frank has reported hyperestrinemia with low estrogen excretion (205).

(*b*) Similar syndromes have been induced in women by large doses of estrogens (162).

(*c*) Hamblen found increased excretion of pregnandiol in a case of pre-menstrual tension (199).

These observations lend themselves to the interpretation that pre-menstrual tension can be attributed to over-stimulation by estrogens or by progesterone or by both hormones. If we accept the theory of overstimulation by the gynecogens, then testosterone is the logical therapeutic agent to be used since it counteracts their biologic effects.

Pre-menstrual mastalgia and mastopathies. It is generally accepted at present that the ducts and acini of the breasts undergo proliferation in response to estrogen and progesterone stimulation during the menstrual cycle (206–213). The proliferation of the ducts becomes noticeable about the mid-menstrual period and acinar growth occurs during the luteal phase of the cycle. With menstruation there occurs a round cell infiltration of the stroma of the lobules and regression of the ductular epithelium, followed by reduction in the size of the acini. In addition to these histologic changes, there is evidence of increased blood supply to the breasts during the pre-menstrual phase which is manifested by prominence of the superficial veins. In many normal women, these histologic and vascular changes cause variable degrees of swelling of the breasts associated with a sensation of firmness, heaviness and tenderness. At the same time, the nipples not infrequently become slightly enlarged and tender. With the onset of menstruation these phenomena subside and recur again during the latter part of the next cycle. In some women these cyclical breast changes are markedly increased in duration and intensity. The breasts begin to become enlarged as early as the 10th day of the cycle and progressively increase in size, accompanied by lancinating pains, extreme tenderness and, frequently, the development of firm, tender lumps. The chronologic relationship of these phenomena to the production of estrogens and progesterone by the ovary and the striking relief which begins to occur as soon as menstruation commences, taken in conjunction with the demonstrated proliferative effect of both estrogens and progesterone on breast tissue, logically leads to the conclusion that the pre-menstrual mastalgia and mastopathies are the result of excessive stimulation by estrogens and/or progesterone. When testosterone propionate is administered, in adequate dosage, the relief or prevention of the symptoms is so prompt and complete (even to the abolition or prevention of the recurring lumps), that it suggests an inactivation of the estrogens and/or progesterone.

The therapeutic effectiveness of testosterone propionate in controlling cyclical mastopathies was first reported by Demarest and Capitain (20) and has been confirmed by others since (6, 21). The mechanism may be a direct effect on the breast, counteracting the proliferative and vascular stimulating action of the gynecogens—or the effect may be mediated through the ovary, causing a reduction in the production of estrogens and progesterone. The promptness with which the pain and swelling subside after a few injections of testosterone propionate and the evidence of striking regressive changes induced by testosterone propionate on other epithelial structures that are responsive to the growth promoting influence of the estrogens and progesterone (the endometrium and vaginal mucosa), suggest that the testosterone probably has a similar direct inhibitory action on the breast. It is interesting, in this connection, to note that in contrast to this inhibitory action in the human female, in rats a number of androgens cause hypertrophy of the breasts (35, 38, 51, 57, 117–119) and, in monkeys, proliferation of duct epithelium (123) and alveolar growth (122, 124).

Methyl testosterone, administered orally, or by skin inunction, is also effective whereas ethinyl testosterone (pregneninolone) is noticeably less effective in relieving and preventing the pre-menstrual mastalgias and mastopathies. The latter, however, has been used with gratifying results in cases in which the presence of hypertrichosis or acne precluded the use of testosterone propionate or methyl testosterone. As has been mentioned above, pregneninolone has no biologically demonstrable anti-gynecogenic action and no arrhenomimetic potency, nor does it inhibit the gonadotrophic activity of the hypophysis. Its action must, therefore, be a direct one on the breast tissue.

Lactation. Inhibition of lactation by means of testosterone propionate has been reported by a number of investigators (214–217). The writer has obtained equally good results with methyl testosterone, started immediately after delivery. Ethinyl testosterone, was definitely less effective. The suppression of lactation can be attributed to hypophyseal inhibition of the prolactin factor or to a direct inhibitory effect on the mammary tissues, or to both.

Intermenstrual (ovulation) bleeding and ovulation pain (Mittelschmerz). Occasionally, intermenstrual bleeding or staining is associated with, or preceded by quite severe right or left lower quadrant abdominal pain. Both phenomena are ascribable to some abnormality in the development of the graafian follicle. The

ovary is usually enlarged to approximately twice its normal size and is exquisitely tender. It is common knowledge that the pain is frequently caused by some bleeding from the ruptured graafian follicle. The mechanism of the endometrial bleeding is not clear. Once the symptoms have appeared, testosterone propionate, in our experience, does not prove effective. But both the pain and bleeding can be prevented if testosterone is administered during the first week or ten days of the cycle. This suggests an inhibitory action on the hypophysis, although a suppressive action on the growth of the follicle cannot be excluded. It is significant that this degree of inhibition can be achieved without suppressing the next menstrual period. In 4 cases that had been treated for 3 successive cycles, the symptoms did not recur during the post-therapy period, which varied from 9 to 32 months. In 2 of these, however, suppressive doses were employed. In several cases, the effects of the therapy wore off within 2 or 3 months and symptoms recurred. In such cases, small doses may have to be administered repeatedly with each cycle. Methyl testosterone has proved effective in 3 cases treated by the writer. In the same patients, pregneninolone (ethinyl testosterone) had no effect on the symptoms.

Endometriosis. If the disease is detected in its early stages (when the diagnosis is admittedly difficult to make), treatment with testosterone propionate, for theoretical reasons, should prove of value. The rationale for this therapy is based on the generally accepted view that the progress of the disease is essentially dependent upon the growth stimulating effect of estrogens and progesterone upon endometrial tissue. By inhibiting the proliferative process in the early stages of the disease and inducing, for a sufficiently prolonged period, atrophy of the ectopic endometrial tissue, the progress of the disease may be aborted. In view of the progressive character of this disease, particularly in young women, androgen therapy merits a thorough trial. The writer has used testosterone propionate with encouraging results, pre- and post-operatively, in patients in whom conservative surgical measures were necessary because of the importance of preserving reproductive function. Unremitting care in the regulation of the dosage (with constant control by vaginal smears) is essential, since one must keep the patient supplied with androgens up to the limit of her tolerance. Inasmuch as this brings one close to the threshold of arrhenomimetic effects, the necessity for constant control by morphologic studies is obvious.

Evaluation of estromimetic action of testosterone propionate in menopause therapy. In 1936, Moquot and Moricard (1, 2) reported relief of post-castration urinary symptoms and flushes with testosterone acetate. The authors described clinical improvement (with as little as a single 5 mg. injection) in some cases and, in others, intensification of the nervous instability. They attributed the therapeutic effect to a direct action of the testosterone acetate upon the superior cervical ganglion which in turn acted upon the hypophysis. The writer began using androgens early in 1936 in the experimental treatment of dysmenorrhea, menorrhagia and the menopause syndrome. Employing the androgens of low potency which were available at that time (androsterone and dehydroandrosterone benzoate), and later testosterone, the clinical results were not sufficiently striking or uniform to permit definite conclusions. When testosterone propionate became available, preliminary studies were conducted to explore its endocrinologic properties in the human female. It was only after hormonologic and morphologic studies began to reveal objective evidence of biologic effectiveness that we began to seriously appraise the therapeutic properties of testosterone propionate.

In 1937, the writer (3) reported that testosterone propionate, administered to a female surgical castrate, simulated biologically and clinically the effects of estrogen administration. The patient's symptoms were relieved, the gonadotrophic hormone excretion reduced and the vaginal smears showed estromimetic effects. These effects were produced by means of large doses of the hormone (860 mg.). A number of clinical reports have since appeared extolling the therapeutic properties of testosterone propionate in the treatment of the menopause syndrome (4, 5, 17, 218). The impression was created by several reports that testosterone propionate and estrogens can be used interchangeably in menopause therapy with equally satisfactory results. This is erroneous. In the majority of menopausal patients, the therapeutic effectiveness of testosterone propionate is distinctly inferior to that of the estrogens. And the reason for this is that, in the vast majority of menopausal patients, most of the symptoms are caused by an estrogen deficiency. And, whereas, testosterone propionate may exhibit estromimetic activity, this property becomes manifest only if the hormone is administered in highly concentrated doses for prolonged periods of time. The estrogenic effectiveness of testosterone propionate (as estimated by vaginal smear reactions in estrogen-deficient women) is, per unit of weight, considerably less than 1/1000 that of α-estradiol. Administering testosterone propionate in order to produce the therapeutic effect of estrogens is, therefore, an exceedingly impractical and expensive form of therapy. Obviously the estromimetic action of testosterone propionate is chiefly a matter of academic interest and has little, if any, utility in the practical therapy of the menopause.

Significance of gonadotropic hormone excretion in relation to androgen therapy. Another fact which has

contributed to a misconception of the role of androgens in menopause therapy has been the demonstration that testosterone propionate can inhibit the gonadotropic hyperactivity of the hypophysis of the human female castrate (3, 170). Application of this observation to the problem of the menopause would seem to be a logical step.

Undoubtedly, the hypersecretion of gonadotropic hormone can be reduced by testosterone propionate, but only by means of large doses administered for prolonged periods—a dilettante method of achieving an objective which is, per se, of dubious therapeutic value. Furthermore, the part played by the hypersecretion of gonadotropic hormone by the hypophysis in the causation of the menopause symptoms is, at present, not quite clear. Excessive amounts of gonadotropic hormone have been found in the urine of women without the characteristic menopause symptoms and, contrariwise, some of the most severe cases have shown very low gonadotropic hormone titers (219–221). Furthermore, satisfactory therapeutic results have been observed in patients who were still excreting considerable amounts of gonadotropic hormone. In view of the fact, therefore, that suppression of the excessive gonadotropic hormone excretion is a theoretical desideratum of dubious value and that administering testosterone propionate is a slow and expensive method of achieving this hypothetical objective, androgens cannot be logically considered as a substitute for estrogens on the basis of their pituitary inhibiting property.

Modus Operandi of Androgens in Menopause Syndrome

Androgens have been found very helpful in some menopause syndromes in which estrogens alone have proved either ineffective or have actually aggravated some of the symptoms. Several years ago, the observation was made that in some menopausal patients with severe symptoms the vaginal smears revealed no evidence of estrogen deficiency (220). Furthermore, such patients excrete estrogens in considerable amounts, even in the absence of ovaries (222, 223). In addition, there is a group of patients who have most distressing symptoms of the menopause in spite of the fact that they menstruate regularly. In some instances, these symptoms have been found associated with normal cyclical endometrial patterns, indicating apparently normal estrogen and progesterone production by the ovary. In the latter group, treatment with estrogens causes profuse uterine bleeding and, in some cases, induces hyperestrogen (tension) symptoms. Both types of menopause symptoms are dramatically relieved by testosterone propionate. And, it is worthy of note that the spectacular therapeutic effect is achieved with doses which are so small (10 to 25 mg., 2 or 3 times weekly) that it cannot be attributed to an estromimetic action or to inhibition of the hypophysis.

What is the explanation for this therapeutic effect? It is apparent that in these cases the basic disturbance is not an estrogen deficiency. For reasons to be discussed later, the writer has hypothesized the participation of endogenous androgens in the sex-hormone organization of the normal cyclical female—their function being to counterbalance the action of the gynecogens. In the majority of menopausal (or ovariectomized) patients, an estrogen deficiency develops which is reflected in regressive changes in the endometrium and vaginal mucosa and is associated with the characteristic symptoms. In a smaller group of patients, certain menopause symptoms are associated with cyclical, morphologic and hormonal evidence indicating a sufficiency of estrogens. In this group, the writer has postulated the existence of an androgen deficiency as the cause of the symptoms. It is interesting, in this connection, to note that Dingemanse and his coworkers (224) have found low androgen excretion in aged females (as well as males) and Hamblen et al. (225), low androgen excretion in patients after hysterectomy and bilateral oophorectomy but relatively high titers during and after the climacteric. In the present unsettled state of our knowledge of androgen metabolism and the variations in androgen determination methods and excretion values, it is difficult to evaluate the significance of these studies. However, if we accept the hypothesis of an androgen deficiency in some types of menopause patients, then one can understand the striking therapeutic effectiveness of testosterone propionate in contrast to the ineffectiveness of estrogen therapy in this group of patients.

Physiological Implications of Androgen Therapy

On reviewing the protean endocrinologic effects of androgen administration to women, it becomes apparent that there is a progressive sequence in the development of the morphologic changes and of the arrhenomimetic phenomena, which is governed by the dose of hormone administered. The small doses produce no demonstrable interference with the normal cyclical, morphologic or hormonal phenomena; larger doses cause, *a*), inhibition of the gonadotropic activity of the hypophysis with consequent failure of ovulation to occur, and *b*), suppression of estrogen and progesterone formation by the ovary, leading to failure of the endometrium and vaginal mucosa to proliferate in the normal physiologic manner and resulting in suppression of menstruation. Further administration of the hormone leads to progressive involution of the genital tract and the development of arrhenomimetic phenomena. The approximate threshold

levels have been determined for the suppression of menstruation and the associated regressive changes in the endometrium and vagina, and for the arrhenomimetic effects. Fortunately, the amount of hormone required for therapeutic purposes, in the average case, is well below this threshold. So that, if one is careful in the selection and observation of the patients and one controls each case with appropriate morphologic studies, virtually no danger of inducing the arrhenomimetic phenomena exists. It should be pointed out, however, that whereas this is true of the average case, there is some variation in individual susceptibility to the hormone and, for this reason, such cases should be observed carefully during the period of androgen administration.

Mechanism of endometrial and vaginal involution induced by androgens. The involution which is induced in the genital tract of cyclical women by testosterone propionate calls for a discussion of the mechanism whereby these spectacular phenomena are produced. The atrophy in the endometrium and vagina is of such striking degree and develops so rapidly that it cannot be attributed solely to the suppression of estrogen production during the current cycle. In an histological study of the vaginal mucous membrane of a series of 68 cases of post-menopausal and surgically castrated women, we did not find vaginal atrophy within 2 months after cessation of menstruation or removal of both ovaries. Furthermore, it was not unusual to find well-preserved vaginal mucosa as long as 28 months after surgical removal of both ovaries. Apparently, the involution process, which is set in motion after the source of physiologic estrogens in the body is removed or ceases to function normally, proceeds at a very slow pace, requiring, in most cases, many months before atrophy develops. In order to account, therefore, for the striking involution which can be induced within 4 to 6 weeks in the endometrium and vaginal mucosa with testosterone propionate, we must postulate the participation of other factors in addition to estrogen deprivation. In the light of our studies, we suggest the following: *a*), a direct inhibitory action of testosterone propionate upon the proliferative capacity of the epithelial elements in the endometrium and vagina; and *b*), direct inactivation of the circulating or stored physiologic estrogens in the body. It is not unlikely that basically the action of testosterone is a uniform one, consisting of inhibition of the functional and proliferative activity of all the epithelial elements participating in the normal sex hormone cycle, i.e., those of the hypophysis, ovaries, uterus and vagina.

Relationship of androgen therapy to fertility. A fact of considerable significance, which has previously been pointed out, but merits stressing, is the transitory character of the morphologic changes in the genital tract induced by testosterone and the amazing rapidity with which restitution to normal occurs even after enormous doses. The restoration of the normal cyclical phenomena in the endometrium associated with cyclical bleeding in patients for as long as 3 years after such suppression and the occurrence of normal pregnancies and offspring indicate that there is a complete physiological restitution of the hypophysis-ovary-uterus relationship.

Paradoxical action of testosterone propionate in the menopause. It is apparent that in contrast to its bisexual activity in animals, testosterone propionate produces effects in cyclical women that are uniformly anti-gynecogenic. In estrogen deficient women (post-menopause or castrated), if administered in sufficient amounts, testosterone propionate exerts an estromimetic action. With our present limited knowledge of the metabolism of the sex sterols, an explanation of this paradoxical action of testosterone must be regarded as highly speculative. It is conceivable that in the presence of an estrogen deficiency the metabolism of administered androgens may differ from that which prevails when the body is supplied with a sufficiency of endogenous gynecogens. That some such difference exists is indicated by the fact that the doses of testosterone propionate which are arrhenomimetic (500 to 600 mg. in one cycle) in cyclical women, have no such effect in post-menopause and castrated women. In these estrogen-deficient patients the administered androgens may be converted to estrogens. In favor of this view can be cited the observations that there is an increased excretion of estrogens in rats (226), in men (227, 228) and in castrated women (170) after treatment with androgens.[1]

Apparently, in the presence of a well-defined estrogen deficiency (whether due to the climacteric or bilateral ovariectomy), administration of large doses of androgens results in estromimetic effects and in the excretion of estrogens. It is conceivable that the metabolism of the sex sterols is so altered as a result of (ovarian) estrogen deprivation that, in the estrogen deficient individual, androgen administration results in the conversion of androgens to estrogens. In the cyclical female with adequate gynecogen production by the ovaries this apparently does not occur and the androgens have a uniformly antigynecogenic action.

Physiological implications of androgen therapy. As one reviews the complex and dramatic biologic and therapeutic properties of teetosterone propionate, one cannot avoid the implication that, in the normal human female, endogenous androgens may perform similar

[1] On the other hand, Kochakian (229) failed to find increased excretion of estrogens in the urine of dogs after androgen injections. LaRoche, Simmonet and Bompard (230) failed to find any increase in estrogens in ovariectomized women after treatment with testosterone propionate. The data published by the latter is, however, insufficient to permit of evaluation of their reports.

functions. There are a number of observations that support the theory that androgens play a physiologic role in the sex hormone organization of the human female. Thus it has been shown that normal adult women excrete significant amounts of androgens (231–233) (26 I.U. per day as compared with an average of 40 I.U. per day by males), which are chemically identical with the androgens excreted by males (234, 235); whereas, the androgen excretion before puberty is extremely small (1.8 to 2 I.U. per liter) (233). Apparently, androgens assume physiologic importance coincidentally with the establishment of the complex sex hormone relations associated with menstruation. The anti-gynecogenic properties of testosterone propionate in cyclical women and its effectiveness in cases presenting symptoms attributable to excessive or abnormal gynecogenic stimulation, suggests that in normal women androgens have an anti-gynecogenic function and that, in certain gynecologic disorders, this function is either defective or deficient. As to the source of the endogenous androgens, the evidence points to the adrenal cortex. Thus it has been shown that the adrenal cortex contains androgens (236–238); that excretion of androgens continues after oophorectomy (239, 240) or orchidectomy but is diminished in Addison's disease (239).

In the normal, sexually mature woman, gynecogens and androgens are conceived as being in a state of dynamic balance, giving rise to the normal female secondary sex characteristics and normal menstruation. The equilibrium may, however, be upset in one direction or the other. If the gynecogens become dominant, either as a result of a qualitative or quantitative deficiency in androgens, or because of an excessive production of gynecogens, the resulting imbalance would be manifested clinically by menorrhagia, metrorrhagia, pre-menstrual tension, mastopathies and dysmenorrhea, separately or in various combinations. If, on the other hand, the androgen influence were to predominate, the clinical picture would consist of oligomenorrhea or amenorrhea and arrhenomimetic phenomena. It is obvious that in such a dynamic system similar biologic and clinical effects would result from an excess of the one as from a deficiency of the opposing factor. It is tempting to accept this theory of a dynamic gynecogen-androgen balance since it appears, at present, to offer a solution to the riddle of functional gynecologic disorders.

REFERENCES

1. Mocquot, P., and R. Moricard: *Bull. Soc. de Gynec. et d'Obst.* 25: 787. 1936.
2. Mocquot, P., and R. Moricard: *Ibid.* 25: 791. 1936.
3. Salmon, U. J.: *Proc. Soc. Exper. Biol. & Med.* 37: 488. 1937.
4. Kurzrok, L., C. H. Birnberg, and S. Livingston: *Endocrinology* 24: 347. 1939.
5. Silberman, D., H. M. Radman, and A. R. Abarbanel: *Am. J. Obst. & Gynec.* 39: 332. 1940.
6. Loeser, A. A.: *Lancet* 1: 373. 1938.
7. Foss, G. L.: *Lancet* 1: 992. 1938.
8. Geist, S. H., U. J. Salmon, and J. A. Gaines: *Endocrinology* 23: 784. 1938.
9. Beclere, C.: *Bull. Soc. de Gynec. et d'Obst.* 27: 749. 1938.
10. Mazer, C., and M. Mazer: *Endocrinology* 24: 599. 1939.
11. Sturgis, W. C., A. R. Abarbanel, and D. S. Nader: *Am. J. Obst. & Gynec.* 39: 102. 1940.
12. Bravaski, J.: *Bull. Soc. de Gynec. et d'Obst.* 28: 418. 1939.
13. Desmarest, E., and Capitain: *Presse med.* 51: 1031. 1939.
14. Abarbanel, A. R.: *Am. J. Obst. & Gynec.* 39: 243. 1940.
15. Turpault, M.: *Gynecologie* 38: 281. 1939.
16. Mascio, A.: *Fol. demograph-gynaec.* 36: 165. 1939.
17. Birnberg, C., L. Kurzrok, and C. Livingston: *Endocrinology* 23: 243. 1938.
18. Salmon, U. J., S. H. Geist, and R. I. Walter: *Am. J. Obst. & Gynec.* 38: 264. 1939.
19. Rubinstein, H. S., and A. R. Abarbanel: *Am. J. Obst. & Gynec.* 37: 707. 1939.
20. Desmarest, E., and Capitain: *Presse med.* 45: 777, 1109. 1937; 46: 185. 1938.
21. Douay, M.: *Compt. rend. Soc. franc. de Gynec.* 8: 165. 1938.
22. Kurzrok, R., and C. P. O'Connell: *Endocrinology* 23: 476. 1938.
23. Birnberg, C. H., L. Kurzrok, and S. J. Klor: *Am. J. Obst. & Gynec.* 39: 107. 1940.
24. In Press.
25. Ihrke, I. A., and F. E. D'Amour: *Am. J. Physiol.* 96: 289. 1931.
26. Browman, L. G.: *Proc. Soc. Exper. Biol. & Med.* 36: 205. 1937.
27. Robson, J. M.: *J. Physiol.* 92: 371. 1938.
28. Courrier, R., and G. Cohen-Solal: *Compt. rend. Soc. de biol.* 124: 925. 1937.
29. Van der Woerd, L. A.: *Acta. neerl. Physiol.* 7: 1. 1937.
30. Robson, J. M.: *Quart. J. Exper. Physiol.* 26: 355, 1937.
31. Leonard, S. L., V. Sager, and J. B. Hamilton: *Proc. Soc. Exper. Biol. & Med.* 37: 362. 1937. 1940.
32. Davids, A. M., and Rubin, I. C.: *Endocrinology* 26: 523. 1940.
33. Robson, J. M.: *Proc. Soc. Exper. Biol. & Med.* 35: 49. 1936; *J. Physiol.* 90: 15. 1937.
34. Cotte, G., and R. Noel: *Gynec. & Obst.* 34: 294. 1936.
35. Nelson, W. O., and C. G. Merckel: *Proc. Soc. Exper. Biol. & Med.* 36: 823. 1937.
36. Hohlweg, W.: *Klin. Wchnschr.* 16: 586. 1937.
37. McEuen, C. S., H. Selye, and J. B. Collip: *Proc. Soc. Exper. Biol. & Med.* 36: 390. 1937.
38. Korenchevsky, V., M. Dennison and K. Hall: *Biochem. J.* 31: 780. 1937.
39. Wolfe, J. M., and J. B. Hamilton: *Proc. Soc. Exper. Biol. & Med.* 37: 189. 1937.
40. Parkes, A. S., and S. Zuckerman: *J. Physiol.* 93: 16. 1938.
41. Fischer, A.: *Rev. franc. d' Endocrin.* 16: 1. 1938.
42. Korenchevsky, V., M. Dennison and J. Bravsin: *Biochem. J.* 30: 558. 1936.
43. Hain, A. N.: *Quart. J. Exper. Physiol.* 26: 293. 1937.
44. Korenchevsky, V.: *Nature* 135: 434. 1935.
45. Korenchevsky, V., M. Dennison and S. L. Simpson: *Biochem. J.* 29: 2534. 1935.
46. Korenchevsky, V., and M. Dennison: *J. Path. & Bact.* 42: 91. 1936.
47. Korenchevsky, V., and K. Hall: *J. Path. & Bact.* 45: 681. 1937.
48. Deanesly, R., and A. S. Parkes: *Quart. J. Exper. Physiol.* 26: 393. 1937.
49. Deanesly, R., and A. S. Parkes: *Brit. M. J.* 1: 257. 1936.
50. Tschopp, E.: *Arch. Int. de Pharm. et Therap.* 52: 381. 1936.
51. Nelson, W. O., and T. F. Gallagher: *Science* 84: 230. 1936.
52. Butenandt, A.: *Naturwis.* 24: 15. 1936.
53. Butenandt, A.: *Bull. Soc. de chem. Biol.* 19: 1477. 1937.
54. Korenchevsky, V., M. Dennison and M. Eldridge: *Biochem. J.* 31: 467. 1937.
55. Korenchevsky, V.: *Nature* 137: 494. 1936.

56. KORENCHEVSKY, V., AND M. DENNISON: *J. Path. & Bact.* 43: 345. 1936.
57. PHELPS, D., J. C. BURCH AND E. T. ELLISON: *Endocrinology* 23: 458. 1938.
58. BUTENANDT, A., AND H. KUDZUS: *Ztschr. f. physiol. Chem.* 237: 75. 1935.
59. SALMON, U. J.: *Proc. Soc. Exper. Biol. & Med.* 38: 352. 1938.
60. SALMON, U. J.: *Endocrinology* 23: 779. 1938.
61. HOHLWEG, W.: *Klin. Wchnschr.* 16: 586. 1937.
62. RUBINSTEIN, H. S., A. R. ABARBANEL AND D. N. NADER: *Proc. Soc. Exper. Biol. & Med.* 39: 20. 1938.
63. NATHANSON, I. T., C. C. FRANSEEN AND A. R. SWEENEY: *Proc. Soc. Exper. Biol. & Med.* 39: 385. 1938.
64. LEATHEM, J. H., AND W. F. STARKEY: *Proc. Penn. Acad. Sci.* 13: 51. 1939.
65. KORENCHEVSKY, V., M. DENNISON AND M. ELDRIDGE: *Biochem. J.* 31: 31. 1937.
66. COURRIER, R., AND G. GROS: *Compt. rend. Soc. de Biol.* 127: 921. 1938.
67. KLEIN, M., AND A. S. PARKES: *Chem. & Ind.* 55: 236. 1936.
68. KLEIN, M., AND A. S. PARKES: *Proc. Roy. Soc., London (B)* 121: 574. 1937.
69. NEUMANN, H. O.: *Ztschr. J. Geburtsh.* 101: 352. 1932.
70. GROHER, H.: *Arch. Gynecologie* 165: 347. 1938.
71. CASTELNUOVO, G.: *Riv. Biol.* 23: 365. 1937.
72. REGNIER, M. T.: *Compt. rend. Acad. de Sci., Paris* 205: 1451. 1937.
73. REGNIER, M. T.: *Bull. Biol. France et Belge* 72: 385. 1938.
74. KOBAYASHI, H.: *Okayama-Igakkai-Zasshi* 43: 3114. 1931.
75. SCHOELLER, W., AND M. GEHRKE: *Arch. f. Gynäk.* 155: 234. 1933.
76. LUDWIG, F., AND J. v. RIES: *Zentralbl. f. Gynäk.* 2366. 1938.
77. TRAINA-RAO, G., AND A. DE PALO: *Ann. Ostetr.* 60: 901. 1938.
78. ZUCKERMAN, S.: *Lancet* 233: 676. 1937.
79. COTTE, G., J. F. MARTIN AND E. MANKIEWICZ: *Gynecologie* 36: 561. 1937.
80. MAZER, M., AND C. MAZER: *Endocrinology* 24: 175. 1939.
81. BOLING, J., AND J. B. HAMILTON: *Anat. Rec.* 73: 1. 1939.
82. SELYE, H.: *Endocrinology* 24: 208. 1939.
83. MIGLIAVACCA, A.: *Bull. Soc. med. chir. Pavia* 44: 433. 1930.
84. MIGLIAVACCA, A.: *Riv. ital. ginec.* 11: 415. 1930.
85. MIGLIAVACCA, A.: *Bull. Soc. ital. Biol. sper.* 5: 1082. 1930.
86. SHAPIRO, H. A., AND H. ZWARENSTEIN: *J. Physiol.* 89: 38. 1937.
87. STARKEY, W. F., AND J. H. LEATHEM: *Proc. Soc. Exper. Biol. & Med.* 39: 218. 1938.
88. FREED, S. C., J. P. GREENHILL AND S. SOSKIN: *Proc. Soc. Exper. Biol. & Med.* 39: 440. 1938.
89. PARKES, A. S., AND S. ZUCKERMAN: *J. Physiol.* 93: 16. 1938.
90. WOLFE, J. M., AND J. B. HAMILTON: *Endocrinology* 21: 603. 1937.
91. WOLFE, J. M., AND J. B. HAMILTON: *Proc. Soc. Exper. Biol. & Med.* 36: 307. 1937.
92. KORENCHEVSKY, V., R. BURBANK AND K. HALL: *Ergebn. Vit. u. Hor. Forschung* 2: 454. 1939.
93. EVANS, H., AND M. E. SIMPSON: *Am. J. Physiol.* 89: 371. 1929.
94. EVANS, H., AND M. E. SIMPSON: *Ibid.* 89: 375. 1939.
95. EVANS, H., AND M. E. SIMPSON: *Ibid.* 89: 379. 1929.
96. HOHLWEG, W., AND M. DOHRN: *Klin. Wchnschr.* 11: 233. 1932.
97. WOLFE, J. M.: *Proc. Soc. Exper. Biol. & Med.* 32: 757. 1935.
98. WOLFE, J. M.: *Proc. Soc. Exper. Biol. & Med.* 32: 1192. 1935.
99. HASHIMOTO, H.: *Mitt. med. Ges., Tokyo* 51: 740. 1937.
100. FRANCK, S.: *Acta. path. Scandinav.* 14: 339. 1937.
101. HERTZ, R., AND R. K. MEYER: *Endocrinology* 21: 756. 1937.
102. CUTULY, E., AND E. C. CUTULY: *Endocrinology* 22: 264. 1938.
103. CUTULY, E., AND E. C. CUTULY: *Ibid.* 22: 568. 1938.
104. BOTTOMLEY, A. C., AND S. J. FOLLEY: *J. Physiol.* 94: 26. 1938.
105. HOHLWEG, W.: *Klin. Wchnschr.* 92: 13. 1934.
106. HALPERN, S. R., AND F. E. D'AMOUR: *Proc. Soc. Exper. Biol. & Med.* 32: 108. 1934.
107. CRAMER, W., AND E. S. HORNING: *Lancet* 230: 247. 1936.
108. SELYE, H., J. B. COLLIP AND D. L. THOMSON: *Proc. Soc. Exper. Biol. & Med.* 32: 1377. 1935.
109. ZONDEK, B.: *Fol. clin. orient.* 1: 1. 1938.
110. HOHLWEG, W.: *Klin. Wchnschr.* 13: 92. 1934.
111. MEYER, R. K., S. L. LEONARD, F. L. HISAW AND S. H. MARTIN: *Endocrinology* 16: 655. 1932.
112. HAMILTON, J. B., AND J. M. WOLFE: *Endocrinology* 22: 360. 1938.
113. BOKSLAG, J. G. H.: *Ergebn. d. Vit. u. Hormon Forschung.* 1939.
114. BOKSLAG, J. G. H., AND L. A. VAN DER WOERD: *Acta. neerl. Physiol.* 8: 9. 1938.
115. WOLFE, J. M., AND J. B. HAMILTON: *Anat. Rec.* 67: 55. 1937.
116. SCHOELLER, W., M. DOHRN AND W. HOHLWEG: *Klin. Wchnschr.* 15: 1907. 1936.
117. SELYE, H., C. S. MCEUEN AND J. B. COLLIP: *Proc. Soc. Exper. Biol. & Med.* 34: 201. 1936.
118. ASTWOOD, E. B., C. F. GESCHICKTER AND E. O. RAUSCH: *Am. J. Anat.* 61: 373. 1937.
119. REECE, R. P., AND J. P. MIXNER: *Proc. Soc. Exper. Biol. & Med.* 40: 66. 1939.
120. JADASSOHN, W., E. UEHLINGER AND A. MARGOT: *J. Invest. Dermat. (Am.)* 1: 31. 1938.
121. BOTTOMLEY, A. C., AND S. J. FOLLEY: *Proc. Roy. Soc. s. B* 126: 224. 1938.
122. GESCHICKTER, C. F., AND E. B. ASTWOOD: *Pub. Am. Assoc. Adv. Sci.* 4: 76. 1937.
123. FOLLEY, S. J., A. N. GUTHKELCH AND S. ZUCKERMAN: *Proc. Roy. Soc. s. B* 126: 469. 1939.
124. VAN WAGENEN, G., AND S. J. FOLLEY: *J. Endocrinol.* 1: 367. 1939.
125. DANTCHAKOFF, V.: *Compt. rend. Soc. de Biol.* 123: 873. 1936; 124: 407, 516; 126: 851; 127: 674, 1255, 1259; 204: 528, 1897; *Bull. biol. des Franc. et Belg.* 71: 269. 1937.
126. GREENE, R. R., AND A. C. IVY: *Science* 86: 200. 1937.
127. GREENE, R. R., M. W. BURRILL AND A. C. IVY: *Proc. Soc. Exper. Biol. & Med.* 38: 1. 1938.
128. HAMILTON, J. B., AND W. U. GARDNER: *Proc. Soc. Exper. Biol. & Med.* 37: 570. 1937.
129. HAMILTON, J. B., AND J. M. WOLFE: *Anat. Rec.* 70: 433. 1938.
130. RAYNAUD, A.: *Bull. biol. Franc. et Belge.* 72: 297. 1938.
131. LIPSCHUTZ, A.: *Arch. Entw.-Mech.* 44: 196. 1916.
132. LIPSCHUTZ, A.: *J. Physiol.* 51: 283. 1917.
133. LIPSCHUTZ, A.: *Compt. rend. Soc. de Biol.* 112: 1272. 1933.
134. SAND, K.: *Arch. f. d. ges Physiol.* 173: 1. 1918–19.
135. MOORE, C. R.: *J. Exper. Zool.* 33: 365. 1921.
136. ROMEIS, R.: *Anat. Anz.* 57: 263. 1923–24.
137. WIESNER, B. P.: *J. Obstet. & Gynec., Brit. Emp.* 41: 867. 1934.
138. HALL, K.: *J. Path. & Bact.* 47: 19. 1938.
139. HAMILTON, J. B.: *Anat. Rec.* 67: 22. 1937.
140. HAMILTON, J. B.: *Endocrinology* 21: 744. 1937.
141. KORENCHEVSKY, V., M. DENNISON AND M. ELDRIDGE: *Biochem. J.* 21: 467. 1937.
142. KORENCHEVSKY, V., M. DENNISON AND M. ELDRIDGE: *Biochem. J.* 21: 475. 1937.
143. LACASSGNE, A., AND A. RAYNAUD: *Compt. rend. Soc. de Biol.* 125: 351. 1937.
144. VIRCHOW, R.: *Virchows Arch. f. path. Anat.* 5: 403. 1853.
145. MARX, L.: *Ztschr. f. Zellforsch. u. micr. Anat.* 16: 48. 1938.
146. KORENCHEVSKY, V.: *Nature* 136: 185. 1935.
147. KORENCHEVSKY, V.: *J. Physiol.* 90: 371. 1937.
148. PRICE, D.: *Am. J. Anat.* 60: 79. 1936.
149. HAMILTON, J. B., AND J. M. WOLFE: *Proc. Soc. Exper. Biol. & Med.* 36: 465. 1937.
150. ALLEE, W. C., AND N. COLLIAS: *Anat. Rec. Sup.* 1 72: 60. 1938.
151. LEONARD, S. L.: *Proc. Soc. Exper. Biol. & Med.* 41: 229. 1939.
152. SHOEMAKER, H. H.: *Proc. Soc. Exper. Biol. & Med.* 41: 299. 1939.
153. BALDWIN, F. M., H. S. GOLDIN AND M. METFESSEL: *Proc. Soc. Exper. Biol. & Med.* 44: 373. 1940.
154. KORENCHEVSKY, V.: *Ergebnisse der Vitamin und Hormon Forschung* 1939.
155. GAINES, J. A., U. J. SALMON AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 38: 779. 1938.
156. SALMON, U. J., R. I. WALTER AND S. H. GEIST: *Proc. Soc. Exper. Biol. & Med.* 39: 467. 1938.

157. Geist, S. H., M. Mintz and U. J. Salmon: *Proc. Soc. Exper. Biol. & Med.* 41: 556. 1939.
158. Geist, S. H., U. J. Salmon, J. A. Gaines and R. I. Walter: *J.A.M.A.* 114: 1539. 1940.
159. Geist, S. H., J. A. Gaines and U. J. Salmon: *Proc. Soc. Exper. Biol. & Med.* 44: 319. 1940.
160. Miescher, K., C. Scholz and E. Tschopp: *Biochem. Ztschr.* 294: 39. 1937.
161. Wilson, L., and R. Kurzrok: *Endocrinology* 26: 587. 1940.
162. Unpublished data.
163. Greenhill, J. P., and S. C. Freed: *J.A.M.A.* 112: 1573. 1939.
164. Thorn, G. W., and G. A. Harrop: *Science* 86: 40. 1937.
165. Thorn, G. W., and L. L. Engel: *J. Exper. Med.* 68: 299. 1938.
166. Thorn, G. W., K. R. Nelson and D. W. Thorn: *Endocrinology* 22: 155. 1938.
167. Kenyon, A. T., I. Sandeford, A. H. Bryan, K. Knowlton and F. C. Koch: *Proc. Soc. Exp. Biol. & Med.* 37: 683. 1938.
168. McCullagh, E. P., and F. J. McGurl: *Endocrinology* 26: 377. 1940.
169. Shorr, E., N. Papanicolaou and F. Stimmel: *Proc. Soc. Exper. Biol. & Med.* 38: 759. 1938.
170. Nathanson, I. T., and L. E. Towne: *Endocrinology* 25: 754. 1939.
171. Rothermich, N. O.: *Endocrinology* 25: 520. 1939.
172. Ruzicka, L., M. W. Goldberg and H. R. Rosenberg: *Helv. Chim. Acta.* 18: 1487. 1935.
173. Foss, G. L.: *Lancet* 1: 992. 1938.
174. Inhoffen, H. H., W. Longemann and A. Serini: *Berl. Deutsch. chem. Ges.* 71: 1024. 1938.
175. Ruzicka, L., K. Hofmann and H. F. Meldahl: *Helv. chem. Acta.* 21: 372. 1938.
176. Inhoffen, H. H., and W. Hohlweg: *Naturwissenschaften* 26: 96. 1938.
177. Emmens, C. W., and A. S. Parkes: *J. Endocrinol.* 1: 332. 1939.
178. Salmon, U. J., and A. A. Salmon: *Proc. Soc. Exper. Biol. & Med.* 43: 709. 1940.
179. Courrier, R., and A. Jost: *Compt. rend. Soc. de Biol.* 130: 1162. 1939.
180. Salmon, U. J., and S. H. Geist: *Proc. Soc. Exper. Biol. & Med.* 45: 522. 1940.
181. Salmon, U. J., R. I. Walter and S. H. Geist: *Proc. Soc. Exper. Biol. & Med.* 40: 252. 1939.
182. Clauberg, C., and Z. Ustun: *Zentralbl. f. Gynäk.* 62: 1745. 1938.
183. Allen, E.: Sex and Internal Secretions, Baltimore, Williams & Wilkins.
184. Corner, G. W.: *Medicine* 12: 61. 1933.
185. Bartelmez, G. W.: *Physiol. Rev.* 17: 28. 1937.
186. Markee, J. E.: *Anat. Rec. Suppl.* 70: 54. 1938.
187. Engle, E. T.: *Cold Spring Harbor Symp. Quant. Biol.* 5: 111. 1937.
188. Ehrenfest, H.: *Am. J. Obst. & Gynec.* 34: 530. 1937.
189. Markee, J. E., J. H. David and J. C. Hinsey: *Anat. Rec.* 64: 231. 1936.
190. Markee, J. E., R. A. Pasqualetti and J. C. Hinsey: *Anat. Rec.* 64: 247. 1936.
191. Daron, G. H.: *Am. J. Anat.* 58: 349. 1936.
192. Contardo, G. B.: *Folia gynaec.* 30: 537. 1933.
193. Frankl, O.: *J. Obst. & Gynec., Brit. Emp.* 40: 397. 1933
194. Mauthner, E.: *Monatschr. f. geburtsh u. Gynäk.* 54: 81. 1921.
195. Reynolds, S. R. M.: Physiology of the Uterus, Hoeber, Inc., 1939.
196. Frank, R. T.: The Female Sex Hormones, Springfield, Thomas, 1929.
197. Zondek, B., S. Rozin and M. Vesell: *Am. J. Obst. & Gynec.* 40: 391. 1940.
198. Zondek, B., and S. Rozin: *J. Obst. & Gynec. Brit. Emp.* 45: 919. 1939.
199. Hamblen, E. C.: *Endocrinology* 24: 269. 1939.
200. Abarbanel, A. R.: *Am. J. Obst. & Gynec.* 39: 243. 1940.
201. Novak, E., and S. R. M. Reynolds: *J.A.M.A.* 99: 1466. 1932.
202. Moir, C.: *Proc. Roy. Soc. Med.* 29: 950. 1936.
203. Lackner, J. E., L. Krohn and S. Soskin: *Am. J. Obst. & Gynec.* 34: 248. 1937.
204. Rubinstein, H. A., and A. R. Abarbanel: *Am. J. Obst. & Gynec.* 37: 709. 1939.
205. Frank, R. T.: *Arch. Neurol. and Psych.* 26: 1053. 1931.
206. Rosenberg, A.: *Frank. Ztschr. f. Path.* 27: 466. 1922.
207. Berberich, J., and R. Jaffe: *Ztschr. f. d. Ges. Anat.* 10: 1. 1924.
208. Dieckmann, H.: *Virchow's Arch. f. path. Anat. u. Physiol.* 256: 321. 1925.
209. Ernst, M.: *Frank. Ztschr. f. Path.* 31: 500. 1925.
210. Mozkowicz, L.: *Arch. f. Klin. Chir.* 142: 374. 1926.
211. Mozkowicz, L.: *Arch. f. Klin. Chir.* 144: 138. 1927.
212. Oliver, R. L., and R. C. Major: *Am. J. Cancer* 21: 1. 1934.
213. Lewis, D., and C. F. Geschickter: *Am. J. Surg.* 24: 280. 1934.
214. Kurzrok, R., and C. P. O'Connell: *Endocrinology* 23: 476. 1938.
215. Abarbanel, A. R.: *Am. J. Obst. & Gynec.* 38: 1043. 1939.
216. Siegler, S. L., and L. M. Silverstein: *Am. J. Obst. & Gynec.* 39: 109. 1940.
217. Birnberg, C. H., L. Kurzrok and S. J. Klor: *Am. J. Obst. & Gynec.* 39: 107. 1940.
218. La Roche, G., H. Simmonet and E. Bompard: *Compt. Rend. Soc. de Biol.* 129: 953. 1938.
219. Frank, R. T., U. J. Salmon and R. Friedman: *Proc. Soc. Exper. Biol. & Med.* 32: 1666. 1935.
220. Salmon, U. J., and R. T. Frank: *Proc. Soc. Exper. Biol. & Med.* 33: 612. 1936.
221. Heller, C. G., and E. J. Heller: *J. Clin. Invest.* 18: 171. 1939.
222. Frank, R. T., M. A. Goldberger and U. J. Salmon: *Proc. Soc. Exper. Biol. & Med.* 33: 615. 1936.
223. Fluhmann, C. F., and K. M. Murphy: *Am. J. Obst. & Gynec.* 38: 778. 1939.
224. Dingemanse, E., H. Borchardt and E. Laquer, *Biochem. J.* 31: 500. 1937.
225. Hamblen, E. C., C. Ashley and M. Baptist: *Endocrinology* 24: 1. 1939.
226. Steinach, E., H. Kun and O. Peczenik: *Wien. Klin. Wchnschr.* 49: 899. 1936.
227. Steinach, E., and H. Kun: *Lancet* 233: 845. 1937.
228. Callow, N. H., R. K. Callow and C. W. Emmens: *Endocrinology* 1: 99. 1939.
229. Kochakian, C. D.: *J. Endocrinol.* 23: 463. 1939.
230. La Roche, G., H. Simmonet and E. Bompard: *Compt. rend. Soc. de Biol.* 130: 521. 1939.
231. Womack, E. B., and F. C. Koch: *Endocrinology* 16: 273. 1932.
232. Kenyon, A. T., T. F. Gallagher, D. H. Peterson, R. I. Dorfman and F. C. Koch: *J. Clin. Invest.* 16: 705. 1937.
233. Koch, F. C.: *Harvey Lectures*, 1937–38.
234. Butenandt, A., and H. Dannenbaum: *Ztschr. f. physiol. Chem.* 229: 192. 1934.
235. Callow, N. H., and R. K. Callow: *Biochem. J.* 32: 1759. 1938.
236. Reichstein, T.: *Helv. Chim. Acta.* 19: 402. 1936.
237. Reichstein, T., and J. V. Euw: *Helv. Chem. Acta.* 21: 1197. 1938.
238. Miescher, K.: *Angewandte Chemie.* 51: 551. 1938.
239. Callow, R. K.: *Proc. Roy. Soc. Med.* 31: 841. 1938.
240. Hamblen, E. C., R. A. Ross, W. K. Cuyler, M. Baptist and C. Ashley: *Endocrinology* 25: 491. 1939.

RATIONALE OF ANDROGENIC THERAPY IN GYNECOLOGY

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BLAIR-BELL (1) has observed appropriately that the older view that *propter ovarium solum, mulier est quod est* is less a real statement of facts than *propter secretiones internas totas, mulier est quod est*. Recent studies upon the physiologic and pathologic aspects of androgenic metabolism continue to emphasize this point of view.

Dr. Geist has described fully his own comprehensive and careful studies of the effects obtained from testosterone propionate in the treatment of various aberrations of gynecic function and, in addition, has summarized the experiences of other workers in this field. He has warned us frequently in his paper that, at present, it is impossible to catalog the various modes of action of androgens in the female and has stated wisely that time and further studies must be awaited for a final evaluation of these as rational therapeutic agents in gynecologic disease. Despite the fact that various animal experiments suggest for these principles the apparent possession of several properties (estrogenic, progestational and androgenic), Dr. Geist's paper indicates that clinically only the androgenic or 'ovarian-negating' and defeminizing one has been established. In this communication, the author will attempt to survey pertinent knowledge available regarding normal and abnormal sex-endocrinology of woman in order to inquire if any rational indications can be established for the use of androgens in gynecic therapy.

Despite the fact that some eight years have elapsed since Womack and Koch (2) demonstrated the presence of androgenic principles in the urine of normal women, little progress has been made in assigning to these substances any definite roles in health and disease of woman. Korenchevsky (3) in 1937 made the following general observations in regard to the nature of studies necessary for the establishment of the clinical significance of androgens in the endocrine economy of woman.

> It is most improbable that the presence of male compounds in the female organ is without significance or without effect on the sexual and other organs and functions; there can be no doubt that they also play an important part in the general endocrinological cooperative and antagonistic activities in the female organism. It follows that the endocrine treatment of diseases of women cannot be perfected until 1) the male sexual hormones present in females have been isolated and identified; 2) a thorough experimental investigation of the physiological properties of these hormones, alone and in combination with estrogenic hormones and progesterone, has been carried out; 3) the normal ratio of estrogenic hormones to progesterone and to male hormones in normal women has been ascertained; 4) the pathological disturbances of this ratio during endocrine and gynecologic disturbances in women have been discovered.

Striking and conclusive as they are, animal experimentation cannot be relied upon to clarify these problems. Engle's (4) pertinent admonition should be heeded: "There is no way to study human physiology other than to study human beings. Experimental animals serve only to prepare the way for human experimentations."

So far, little progress has been made in the solution of the problems enumerated by Korenchevsky. Callow and Callow (5) have identified androsterone and dehydroandrosterone in the urine of normal females. Koch (6) has called attention to the fact that androgens, other than these, are found in the urine of women with virilizing syndomes. The fact has been established by a number of workers (7–10) that large amounts of androgens are excreted in the urine of patients with certain virilizing syndromes.

Approximately 4 years ago our group initiated a diverse and general program of study of the metabolism and excretion of the sex sterols in health and in various diseases of women. A number of reports of various aspects of these studies have appeared; others are in press; additional studies are to be reported. In this communication some of the pertinent data accumulated to date are summarized. During this time a total of 5650 24-hour urines has been titrated for sodium pregnandiol glucuronide (metabolic product of progesterone) by the method of Venning (11) and a total of 5358 24-hour urines has been quantitated for 17-ketosteroids (androgenic metabolic products) by the colorimetric method of Oesting (12). For obvious reasons subsequently mentioned relatively few estrogenic studies were made.

Present Limitations of the Clinical Methods of Study

In general, the studies carried on as a part of this comprehensive program have been characterized by

the application of the available diagnostic methods. Clinical assessment of each patient from the endocrine and gynecologic standpoint was made by the author or under his immediate supervision by his associates. Metabolic, chemical and x-ray examinations were made in detail. Ovario-endometrial correlates were investigated by repeated endometrial biopsies taken within the first 24 hours of spontaneous bleeding. The non-bleeding phases were studied routinely in regard to the urinary excretion of androgens and sodium pregnandiol glucuronide. Daily 24-hour urines were titrated, as a rule, throughout the entire non-bleeding phase of the cycle or for 2 to 3 weeks in non-cyclic patients. Quantitations of estrogens and gonadotropins were made in selected patients. When the metabolism and pharmacologic effects of injections of various of the sex-sterols were under study, pre-treatment levels were established and subsequently hormonal levels during and after therapy were investigated.

Many limitations exist at present with regard to clinical studies of hormonal titers of body fluids. Methods, which yield quite satisfactory results, when relatively few specimens on a small group of patients are examined in the research laboratory, by their very nature and complexities often prove quite impractical when applied to the studies of repeated specimens of large groups of patients. Other shortcomings of these methods will be summarized.

Estrogens. The complexities of estrogenic metabolism, well delineated by Smith and Smith (13), make desirable the quantitation separately of estradiol, estrone and estriol. No satisfactory chemical or colorimetric methods exist. Preliminary differential extractions are complex and time-consuming. It has been suggested that progesterone shifts the reaction estradiol⇆estrone⇄estriol to the right. The workings of injected or intrinsic androgens upon this reaction should be studied. Hoskins and his group (14) have observed an increase in the urinary excretion of estrogens following intramuscular injections of testosterone propionate in males. Gallagher (15) has attributed this increased excretion to an actual synthesis of some of the testosterone propionate injected, into estrogens. Studies of the possible occurrence of such a synthesis in women are being carried out by our group but these have not progressed sufficiently far, as yet, to justify preliminary statements to be made.

Quantitations of estrogenic titers, as well as those of the other sex-endocrine principles in the blood, are completely unsatisfactory as regards the investigation of repeated samples during various phases of the menstrual cycle.

Progesterone (Pregnandiol complex). Biologically active progesterone cannot be recovered from the body fluids of healthy women (16) or after repeated large intramuscular injections of progesterone (17).

The development by Venning (11) of a method for the extraction and gravimetric determination of sodium pregnandiol glucuronide and the clinical applications of this method by Venning and Browne (18) gave promise of proving a valuable means for the evaluation of corpus luteum function. The method, while somewhat laborious, is adaptable to a clinical program of investigation.

Many factors have been encountered which render complex the interpretation of the data obtained by this method. The method of extraction is not exclusive enough to avoid compounds other than pregnandiol complex being recovered; therefore, melting point determinations and crystallization of the precipitates must be made. Alterations in ovarian, endometrial, hepatic and renal functions are reflected in the amount of the compound actually excreted (19). The pregnandiol complex has been recovered from the urine of a patient with an adrenal tumor whose ovaries contained no active lutein tissue (20). Our group (21) on the other hand, has recovered the compound from the urine of a male who was receiving intramuscular injections of desoxycorticosterone acetate. The compound may not be recovered from the urine of patients during cycles prior to bleeding from progestational endometria. Our group (22) has reported its frequent absence from the urine of patients receiving intensive therapy with progesterone. Doubtless, sodium pregnandiol glucuronide is only one of the metabolic products of progesterone. Callow (23) has found that other pregnane derivatives are excreted in the urine; these include allopregnandiol, epiallopregnanolone, two partly investigated pregnantriols and pregnone–3:17:20–triol.

Androgens. Data on the metabolism and excretion of androgens, necessarily pertinent as they are to this discussion, are few for well distributed groups of women. The complex methods of chemical extraction and bioassay which are required for these determinations are not adaptable to routine clinical studies of various groups of women.

The application of the Zimmermann (24) reaction to the quantitation of androgens has been described by Wu and Chou (25), Oesting (26), Callow and Emmens (27) and others. Oesting and Webster (28), employing the extraction method of Gallagher and Koch (29) and a specially designed colorimeter, described a good agreement between results obtained by colorimetric determinations using meta-dinitrobenzene and those from bioassay. Nathanson, Towne and Aub (30) made similar observations. Cuyler and Baptist (31) of our group have described a method of extraction which we have used in conjunction with Oesting's colorimetric technic. Sufficient simplifica-

tion has resulted to permit application to our clinical investigative program.

Many investigators including Koch, have questioned rightly the accuracy and specificity of these methods. In support of the method, may be offered two facts: 1) data secured by it agree well with those secured by methods of bioassay; 2) satisfactory control readings are obtained upon known solutions of androsterone. The chief objections to the method are: 1) the inability to determine qualitatively the various androgens; 2) the uncertainty which exists as to the biologic activity of the 'androgens' (17-ketosteroids) quantitated.

Theoretical Foundations of a Rational Androgenic Therapy

Dr. Geist has described interesting pharmacologic effects which, in a number of groups of patients with certain common symptomatic complexes, produce at times gratifying relief of the undesired symptoms. The objective concomitants of these effects by description and by theory result from the 'ovarian-negating' or active virilizing activity of these agents. By definition a rational sex-endocrine therapy is based upon an accurate diagnosis of hormonopathic factors and is aimed at the restoration of a normal physiologic state. An important aspect of most endocrinopathic disturbances of women is their lowered fertility or actual sterility. A desideratum of rational therapy is the restoration of or the continuation of the fertile state. Do any rational indications exist for the therapeutic employment of androgens in the treatment of women? Certain theoretical indications will be postulated to aid in subsequent discussions.

a) Assuming that androgens act as synergists or pacemakers to the action of the other sex sterols (a fact far from established clinically), theoretically the use of androgens may be rational to supplement androgenic deficits, if these exist as characteristic hormonological accompaniments of endocrine syndromes.

b) Androgens may be of value as rational therapy to curb and balance excessive estrogenic function, if this exists as a clearcut endocrine cause of gynecologic disease.

c) The local use of androgens might prove rational in the treatment of undesired responses or excessive susceptibilities of certain tissues or organs (i.e., the breasts) to normal estrogenic levels. Theoretically antagonistic local effects might be secured without any significant general or constitutional sequelae.

At this point clinical data pertinent to these theoretical indications will be examined.

Androgens in Health

During childhood and adolescence. Androgens are found in the urine of girls even prior to the fourth year of age. The occurrence of a gradual increase in androgenic titers as adolescence and sexual maturity were reached has been observed (28, 30, 32). Nathanson, Towne and Aub found a definite relationship to exist between the titers of urinary androgens, the physical and sexual development and chronologic age of children. Since many workers (6, 23, 33, 34) have submitted evidence that these androgens are formed probably in the adrenals, most likely in the androgenic or x-zone, their increases during growth and sexual maturation cannot be regarded solely as passive concomitants of increasing ovarian function. Their physiologic role during these epochs is unknown. Estimations for mean daily titers vary from 2 I.U. at 3 to 4 years of age to 15 to 23 I.U. at 12 to 14 years of age.

During sexual maturity. Koch (6), calling attention to marked daily fluctuations in androgenic titers of normal women, reported 30 to 100 I.U. to be the average range of variation. In another group investigated the average daily values were given as being 42 to 56 I.U. We have established the average daily urinary titers of a carefully studied group of 13 sexually mature and healthy women to be 34 I.U. (These women had no evidence by history or physical signs of gynecologic or endocrine disease. All excreted normal amounts of sodium pregnandiol glucuronide and all bled from well developed progestational endometria. Androgenic titers were determined daily for at least one complete menstrual cycle.)

No characteristic variations in androgenic titers during various phases of the menstrual cycle have been described (34, 35). Dingemanse and her group (36) reported that the highest androgenic excretion in one patient was observed during the postmenstrual phase of the cycle. Callow (23) has observed a general tendency for higher values to occur the earlier part of the cycle. Our group (37) has reported recently that androgenic titers during bleeding phases of the cycle are lower than during non-bleeding phases. This observation lends support to the theory that bleeding occurs when there exist relatively low levels of the total sterols.

Studies by our group (34) of gynecologic factors influencing the metabolism of androgens have shown that bilateral oöphorectomy produces no significant decrease in androgenic titers (similar observations by Callow, 23) nor does hysterectomy with or without ovarian conservation alter significantly the levels of urinary secretion during the early weeks of postoperative convalescence. This latter observation indicates the non-existence of any endometrial factors such as have been described for estrogens and progesterone.

The effects of injections of testosterone propionate upon the sterol titers of normal women is under investigation. Our group (34) has reported prompt elevation of androgenic titers during these treatments with

the recovery from the urine of amounts varying from 7.6% to 71% of the total androgens given. The effect of this form of treatment upon total urinary estrogens has not been established as yet; studies at present have not progressed sufficiently to warrant reporting. No significant alterations in the urinary titers of sodium pregnandiol glucuronide were produced by a series of injections of androgens in individual doses of 25 mg. given at 2-day intervals for a space of 6 to 10 days during the midmenstrual phase of the cycle (i.e., usually 9th, 11th, 13th, 15th and 17th days of the cycle): for 10 patients treated in this manner for 13 cycles, it was observed that the average total cyclic excretion of the pregnandiol complex was 30 mg. before treatment and 36 mg. during treatment. Correlational endometrial studies agreed with the endocrine ones; an occasional individual experienced definite lowering of hormonal titers of the pregnandiol complex and an interference with the progestational differentiation of the endometrium.

The conclusion may be drawn from these studies that no physiologic role has been established for androgens during the period of sexual maturity. It has been suggested at times by our group that a delicate balance between ovarian estrogens and adrenal androgens exists during sexual maturity and that, as long as ovarian function is good, the influences of androgens are kept in check. Doubtlessly there is such a propitious estrogen:androgen ratio but individual variations and the short-comings of present methods of quantitation render it quite impossible to assign with certainty a normal ratio or to diagnose an abnormal one in most instances. Our group (38) has suggested, upon the basis of observations that a tendency apparently existed for brunettes to excrete larger quantities of androgens than blondes and upon the basis of the 'photographic' properties of androgens described by Hamilton and Hubert (39) in males, that androgens might play a definite role in determining the complexional coloring of women.

In pregnancy no significant alterations have been shown to occur in androgenic titers and no definite physiologic functions have been attributed to these principles. Dingemanse and her group (40) stated that the average excretion ranged from 30 to 60 I.U. per liter of urine. Callow (23) has stated that the values varied from 5 to 60 I.U. per day. Hain (41) found these values to range from 9 to 14 I.U. per day. These data indicate that androgens take no part in the general hormonal plethora of pregnancy. Hain considered that they played no significant part in the specific hormonology of gestation.

During sexual regression. Our group (34) has reported that urinary androgens tend to show definite increases during the climacteric. The average daily titers of 7 women during the immediate premenopausal period were 72 I.U. Those of 7 women, whose intervals since the menopause ranged from 5 months to 2 years, were 76 I.U. Those of 7 women, whose menses had ceased from 4 to 26 years previously, were approximately 58 I.U.

We have related these increases to two factors: 1) Due to an increasing refractivity of the ovaries to the gonadotropic influences of the pituitary and a consequential decrease in estrogenic levels, the ovario-adrenal balance is upset with the result that, unopposed, the androgenic functions of the adrenals increase. There results, accordingly, an alteration in the estrogenic:androgenic ratio due to an absolute increase in androgens and an absolute decrease in estrogens. 2) The compensatory hyperactivity of the pituitary which results from ovarian failure involves adrenotropic functions as well as gonadotropic ones. No refractivity existing in the adrenals, they respond by an increased secretion of androgens.

We have suggested that this increase in androgens during the climacteric may fulfil a physiologic role. By this means the hyperfunction of the pituitary is curbed and a hormonal stabilization, independent of ovaries, is effected. Correlational studies by our group, of androgenic and gonadotropic titers, bear out such a theory. The regressive sexual alterations characteristic of this epoch may be regarded as being due to two sets of influences: 1) a decrease in estrogenic levels and 2) the defeminizing effects of increased androgens.

These findings and the theory offered in explanation of them suggest a possible rational therapeutic use of androgens. In the postmenopausal stage of the climacteric when distressing symptoms continue to occur, gonadotropic titers remain elevated and regressive changes are minimal, controlled androgenic therapy to stabilize the endocrine system would seem to be in line with the physiologic mechanism. Regressive alterations produced by this form of therapy would not have the same significance as when they are induced in women during sexual maturity. In the earlier stages of the climacteric, especially when this process begins somewhat earlier than desired, estrogens should be employed, if any endocrine therapy is deemed necessary. Estrogens given intensively during the postmenopausal phase of the climacteric, however may impede the natural course of sexual aging, for it has been shown by our group (42) that this form of therapy definitely reduces androgenic titers.

Androgens in Disease

Virilizing syndromes. The occurrence of increased androgenic titers in certain of these conditions has been cited previously. No pertinent implications exist as to androgenic therapy, except that androgenic therapy if pursued intensively produces virilizing effects.

Dr. Geist's analysis of andromimetic effects carries a warning that individual idiosyncrasies exist and may result in the occurrence of these sequelae even from moderately small doses of androgens.

Hyperovarianism. Despite the fairly frequent use of this term by clinicians, no clear-cut clinical instances exist of complete hyperovarianism. Granulosa cell tumors of the ovary result in definite hyperestrogenism. No discription of androgenic titers in association with this condition has been encountered. Low androgenic values might be expected. Hormonologic considerations might suggest the desirability of negating this hyperestrogenism by androgenic therapy but clinical judgment and gynecologic knowledge of the morbid pathology demand surgical handling of the tumor.

We have studied recently the hormonal titers and specimens of ovarian tissue of a young girl, approximately 5½ years of age, who was thought to have a granulosa tumor of the ovary because of marked sexual precocity and uterine bleeding. Operation failed, however, to disclose any ovarian or adrenal pathology. Hormonal titers studied daily for approximately 4 weeks prior to operation and for another 2 weeks, thereafter, were found to be those of essentially adult character, as regards androgens, estrogens, pregnandiol complex and gonadotropins. It would not seem rational therapy to oppose precocious sexual development in patients of this type with androgens for fear that permanent impairment of ovarian function and fertility might result, if not distressing virilizing signs.

The author agrees with Greenhill and Freed (43) that premenstrual tension does not constitute a definite hyperovarian syndrome. These workers relate the premenstraul distress, commonly referred to as premenstrual tension, to a retention of sodium ions due to premenstrual increases in sex sterols. Frank (44) previously had regarded the symptoms as being due to hyperestrogenism. Androgenic titers under these conditions have not been found to be low; such an occurrence might be expected if hyperestrogenism existed. It is interesting to observe that good subjective responses have occurred from orally administered estriol glucuronide, progesterone (45) and by androgens (Geist).

The author cannot accept the occurrence of a 'Swiss-cheese' type of endometrium to be proof that hyperestrogenism exists despite the many theories which are founded upon this assumption. The endometrial response is hyperestrogenic but no proof exists that any absolute increase in estrogens is associated.

Functional irregularities of uterine bleeding. Various functional irregularities of uterine bleeding, including endocrine sterility, are related to either primary or secondary hypofunction of the ovaries. In none of these conditions has any significant decrease in androgenic titers been observed except in the rare instances in which hypocortical adrenal function was the primary cause of ovarian failure.

A group of 5 women investigated carefully because of endocrine sterility despite cyclic uterine bleeding and no clinical signs of endocrine disease had an average daily excretion of 49 I.U. of androgens. These patients bled from estrogenic endometria or from ones showing minimal progestational differentiation. Their total urinary excretion of sodium pregnandiol glucuronide per cycle was low, ranging from 0 mg. to 21 mg.

A group of 5 women studied intensively because of menorrhagia or metrorrhagia of functional character, characterized by bleeding from estrogenic or poorly differentiated progestational endometria had an average daily excretion of 42 I.U. of androgens.

A total of 23 women with functional amenorrhea of varying durations has been investigated with regard to an androgenic titers; all patients were under menopausal age. The data on these are summarized.

Number of patients	8	9	6
Duration of amenorrhea	2–5 mo.	6–11 mo.	1–5½ yr.
Average androgenic titers	41 I.U.	54 I.U.	81 I.U.

The increase in androgenic titers as the duration of amenorrhea lengthens apparently expresses a progressive ovarian failure. These findings are consistent with those described for the climacteric and are thought to have the same endocrine import.

These observations upon androgenic titers would appear to offer no rationale for the therapeutic use of androgens in these conditions. The ovarian failure which exists as the cause of these irregularities is magnified doubtlessly by the use of androgens. Complete therapy aims at physiologic salvage except in those individuals of climacteric age. The aim of such therapy is to overcome the endocrine disturbance thereby restoring the procreative functions of the patient; if this cannot be done assuredly, there exists the responsibility of not lowering ovarian function any further.

The author (46) was apparently the first to attempt androgenic therapy in the female. He reported that these principles apparently possessed the ability to check excessive uterine bleeding. He did not pursue these studies but for a short time because of the regressive changes in the endometrium which were observed to follow this treatment and because of fear of andromimetic effects.

Dr. Geist's experience in the treatment of menometrorrhagia typifies the depressing effects of these agents on ovarian function. His group of patients was for the most part comprised of those whose endometria showed secretory changes, i.e., those with only moderate or first degree ovarian failure as contrasted with the more severe and more commonly treated

groups whose bleeding occurs from estrogenic endometria (47, 48). In those patients with first degree ovarian failure, however, androgenic therapy was followed by bleeding from various types of estrogenic endometria, including atrophic or hypoestrogenic ones.

If damage to ovarian function is a matter of no concern because of disinterest of the patient in actual or possible fertility, then it seems that the intra-uterine use of small doses of radium as described by Keene and Payne (49) is more rational, effective and perhaps, cheaper therapy. Patients are not exposed to the possible occurrence of andromimetic effects.

The author cannot agree with Greenhill's (50) observations in regard to relative merits of cyclic therapy with estrogens and progesterone as described by him (16), and of androgenic therapy, as described by Geist and his associates (51) in meno-metrorrhagia: "This elaborate form of therapy (cyclic sterols) would not be practical in the private practice of most physicians or even specialists. Certainly the results with androgens are equally as good and less complicated." The author and his group (52) have summarized recently their experience with injected cyclic sterol therapy over a 3-year period which involved the treatment of 46 patients for a total of 193 cycles. The follow-up data on 22 of this group of patients indicate that a net physiologic salvage of 45.5% was secured, i.e., nearly one-half of the group bled regularly from progestational endometria following discontinuation of therapy, whereas, prior to therapy, their bleeding had been of estrogenic character.

Dysmenorrhea. A group of 10 young women investigated during at least one menstrual cycle because of functional dysmenorrhea had average daily androgenic titers of 66 I.U. These elevated values may be considered indicative of some degree of ovarian failure. The existence of any significant ovarian failure is not substantiated by endometrial studies, for all these patients bled from progestational endometria, although frequently sufficient irregularities occurred in the character of histologic differentiation to permit their classification as mixed endometria.

Headache. A group of 19 young women with 'menstrual' headaches were investigated for at least one menstrual cycle. The average daily excretion of androgens for this group was 58 I.U. The average cyclic excretion of the pregnandiol complex for the group was 18 mg. This moderate elevation of androgens in this group may be significant of ovarian failure.

Cyclomastopathy. A group of 8 young women who complained of cyclic pain in their breasts, associated with tender nodules or cysts, was investigated for at least one menstrual cycle. The average daily excretion of androgens for this group was 51 I.U.

Androgenic Therapy in Instances in Which Certain Local Tissues or Organs Give an Excessive or Undesired Response to Normal Estrogenic Influences

There are observed patients in whom certain tissues or organs fail to give a normal response to ovarian influences which are inducing satisfactory reactions in other tissues or organs. Examples of these may be cited: the presence of a rudimentary or infantile uterus in a woman, otherwise well feminized and showing no evidence of ovarian deficiency; the occurrence of unilateral or bilateral hypomastia under similar circumstances; the similar occurrence of marked hypermastia.

The last example cited, i.e., hypermastia or 'diffuse virginal hypertrophy,' may be treated with some degree of success by making use of the regressive alterations which may be induced in mammary tissue by androgens. By this means, theoretically at least, it might be possible to reduce the relatively excessive stimulation produced by the intrinsic estrogens. Intramuscular use of androgens would produce doubtlessly undesired general effects on ovarian function. Local application of androgens in the form of an ointment might permit the attainment of the desired local effects without any appreciable general ones. No significant effects would be expected in the instances where marked hypertrophy existed.

Lactation, at times, may be an undesired response to normal endocrinal stimuli. Kurzrok and O'Connell (53) and others, subsequently have reported that androgens were effective in suppressing lactation. This is to be expected from a consideration of the pharmacologic properties of androgens. Estrogens also suppress lactation (54, 55, 56, and others). It is doubted if any endocrine therapy is necessary to suppress lactation; if so the use of estrogens is to be preferred to taking any chances with the andromimetic effects of androgens.

CONCLUSION

Despite the establishment of the pharmacologic activity of androgens in woman and the observations reported that desirable symptomatic therapy employing them may be permitted in certain gynecologic diseases, a review of our present knowledge of the role of these principles in health and disease of woman delineates few clear-cut indications for the use of androgens in rational therapy. This is not unexpected in view of the defeminizing and 'ovarian-negating' effects produced by androgens. Only two possible rational indications seem to exist: 1) in the postmenopausal stage of the climacteric when spontaneous endocrine stabilization appears delayed and is associated with severe symptomatology and 2) in certain in-

stances of hypermastia, where a local antagonism of estrogenic effects is sought by the application of androgens in ointment form.

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REFERENCES

1. Blair-Bell, W.: *Brit. M. J.* 1:515. 1935.
2. Womack, E. B., and F. C. Koch: *Endocrinology* 16; 273. 1932
3. Korenchevsky, V.: *Brit. M. J.* 2:896. 1937.
4. Engle, E. T.: *Arch. f. Gynäk.* 166: 131. 1938.
5. Callow, N. H., and R. K. Callow: *Biochem. J.* 32: 1759. 1938.
6. Koch, F. C.: *Bull. N. Y. Acad. Med.* 14:655. 1938.
7. Simpson, S. L., P. de Fremery, and A. Macbeth: *Endocrinology* 20: 363. 1936.
8. Slot, W. J.: *Acta. Med. Scandinav.* 89: 371. 1936.
9. Callow, R. K.: *Chem. & Indust.* 14: 1030. 1936.
10. Kenyon, A. T., T. F. Gallagher, D. H. Peterson, R. I. Dorfman, and F. C. Koch: *J. Clin. Investig.* 16: 705. 1937.
11. Venning, E. H.: *J. Biol. Chem.* 1119: 473. 1937; 126: 595. 1938.
12. Oesting, R. B.: *Proc. Soc. Exper. Biol. & Med.* 36: 524. 1937; 39: 76, 1938.
13. Smith, G. V. S., and O. W. Smith: *Am. J. Obst. & Gynec.* 36: 769. 1938.
14. Hoskins, W. H., J. R. Coffman, F. C. Koch, and A. T. Kenyon: *Endocrinology* 24:702. 1939.
15. Gallagher, T. F.: Discussion, section on Pharmacology, The Federation of American Societies for Experimental Biology, New Orleans session, March 15, 1940.
16. Hamblen, E. C.: *Endocrinology* 24: 13. 1939.
17. Hamblen, E. C., W. K. Cuyler, and D. V. Hirst: *Endocrinology* 27: 33. 1940.
18. Venning, E. H., and J. S. L. Browne: *Endocrinology* 21: 711. 1937; *Am. J. Physiol.* 123; 209. 1938.
19. Hamblen, E. C., C. Ashley, and Baptist: *Endocrinology* 24: 1. 1939.
20. Browne, J. S. L., and E. H. Venning: Personal communication of E. H. Venning, March 10, 1939.
21. Cuyler, W. K., C. Ashley, and E. C. Hamblen: *Endocrinology* 27: 177. 1940.
22. Hamblen, E. C., N. B. Powell, and W. K. Cuyler: *Am. J. Obst. & Gynec.* 38: 557. 1939; Hamblen, E. C., W. K. Cuyler, N. B. Powell, M. Baptist, and C. Ashley: *Endocrinology* 25: 13. 1939.
23. Callow, R. K.: *Proc. Roy. Soc. Med.* 31: 841. 1938.
24. Zimmermann, W.: *Ztschr. f. Physiol. Chem.* 233: 257. 1935; 245: 47. 1936.
25. Wu, H., and C. Y. Chou: *Chinese J. Physiol.* 11: 413. 1937.
26. Oesting, R. B.: *Proc. Soc. Exper. Biol. & Med.* 36: 524. 1937; 39: 76. 1938.
27. Callow, R. K., and C. W. Emmens: *Biochem. J.* 32: 1312. 1938.
28. Oesting, R. B., and B. Webster: *Endocrinology* 22: 307. 1938.
29. Gallagher, T. F., and F. C. Koch: *J. Pharmacol. & Exper. Therap.* 55: 97. 1935.
30. Nathanson, I. T., L. E. Towne, and J. C. Aub: *Endocrinology* 24: 335. 1939.
31. Cuyler, W. K., and M. Baptist: *J. Lab. & Clin. Med.*, in press.
32. Dorfman, R. I., W. W. Greulich, and C. I. Solomon: *Endocrinology* 21: 741. 1937.
33. Simpson, S. L.: Personal communication, October 30, 1939.
34. Hamblen, E. C., R. A. Ross, W. K. Cuyler, M. Baptist and C. Ashley: *Endocrinology* 25: 491. 1939.
35. Gallagher, T. F., D. H. Peterson, R. I. Dorfman, A. T. Kenyon, and F. C. Koch: *J. Clin. Investig.* 16: 695. 1937.
36. Dingemanse, E., H. Borchardt and E. Laqueur: *Biochem. J.* 31: 500. 1937; *Schweiz. Med. Wchnschr.* 67: 670. 1937.
37. Hamblen, E. C., W. K. Cuyler and M. Baptist: *Endocrinology* 27: 16. 1940.
38. Hamblen, E. C., and W. K. Cuyler: *J.A.M.A.* 113: 38. 1939.
39. Hamilton, J. B., and G. Hubert: *Science* 88: 481. 1938.
40. Dingemanse, E., H. Borchardt, and E. Laqueur: *Biochem. J.* 31: 500, 1937.
41. Hain, A. M.: *Edinburgh M. J.* 45: 678. 1938.
42. Hamblen, E. C., C. J. Pattee, and W. K. Cuyler: *Endocrinology* 27: 734. 1940.
43. Greenhill, J. P., and S. C. Freed: *Endocrinology* 26: 529. 1940.
44. Frank, R. T.: *Arch. Neurol. & Psychiat.* 26: 1053. 1931.
45. Israel, S. L.: *J.A.M.A.* 110: 1721. 1938.
46. Hamblen, E. C. *J. M. A. Ga.* 26: 368. 1937.
47. Hamblen, E. C.: *South. M. J.* 32: 308. 1939.
48. Hamblen, E. C.: Endocrine Gynecology, Charles C Thomas, Springfield, Illinois, 1939.
49. Keene, F. E., and F. L. Payne: *Surg., Gynec. & Obst.* 56: 322. 1933; *Am. J. Obst. & Gynec.* 34: 688. 1937.
50. Greenhill, J. P.: Year Book of Obst. and Gynec. P. 539, 1939.
51. Geist, S. H., U. J. Salmon, and J. A. Gaines: *Endocrinology* 23: 784. 1938.
52. Hamblen, E. C., W. K. Cuyler, C. J. Pattee, and G. J. Axelson: *Journal of Clinical Endocrinology*, in press.
53. Kurzrok, R., and C. P. O'Connell: *Endocrinology* 23: 476. 1938.
54. Switsky, W.: *Zentralbl. f. Gynäk.* 59: 2784. 1935.
55. Major, J. M.: *Zentralbl. f. Gynäk.* 60: 2379. 1936.
56. Jeffcoate, T. N. A.: *Brit. M. J.* 1: 674. 720. 1937.

COMMUNICATIONS TO THE EDITORS

GOITER, IODINE AND MILITARY STRENGTH

The first public interest in nutrition was initiated by the military leaders during the Boer War and the great impetus to the scientific study of nutrition was from the military leaders during the World War. While serving as Nutrition Officer of the 6th Division, U. S. Regular Army during 1918 the senior author planned a study of goiter and rickets prevention in order to increase the military strength of the nation. He became convinced that goiter is largely due to iodine deficiency, and over the past 20 years has developed methods of iodine analysis in food and water.

Although a barrel of water was necessary for the earlier methods of iodine analysis this quantity has been reduced to a quart. Recently 12 samples of Yancey County, N. C., water were received from Dr. R. O. Jones, district Health Officer. These are tabulated as follows, together with the iodine content in parts per billion (γ/kg.).

Deyton Bend School (spring)	0.13
Burnsville (chlorinated)	0.17
Burnsville (chlorinated)	0.23
Micaville School (spring)	0.20
Bald Creek School	0.51
Clermont School (spring and reservoir)	0.53
Relief School (spring)	0.61
Celo School (spring)	0.65
Bee Log School (spring)	0.66
Indian Creek School (spring)	0.67
Ramseytown School (spring)	0.90
Pensacola School	1.61
Average	0.57

Yancey County, on the Tennessee Border, and containing the highest point of land east of the Mississippi, is in the first section of North Carolina of Davenport and Love (1) and had the highest rate of total goiter per 1,000 drafted men (4.56 compared with a state average of 3.58). The average iodine content is similar to that of Minneapolis tap water (0.43 γ per kg.) and La Grange, Ill. deepwell water (0.59) (2), analyzed by the same method, both of which are in a goitrous region.

These values may be compared to the following non-goitrous regions (3); Atlanta 3.30; St. Louis 3.52; Salina, Kan. 3.91; Baltimore 5.00; Berkeley, Cal. 5.90; New Orleans 7.70; Corona, Cal. 54.58; San Dimas, Cal. 73.30 γ per kg.

Mineral waters in goitrous regions, drunk by relatively few persons or not at all, may be high in iodine. It seems that the iodine in drinking waters and those draining from farm lands or used to water stock would in general bear an inverse relation to goiter.

Some persons drink distilled water or spring water selected for its vanishingly small mineral content. Where water is used merely to replace that lost by evaporation, as in storage batteries, a low mineral content is desirable. But due to the fact that minerals are lost by way of the kidneys, the mineral content of drinking water is important. A spring in Iceland, whose water was said to be purified cryoscopically, was reputed to be poisonous and a number of springs were called 'goiter springs' (as we suspect due to the absence of iodine rather than the presence of a goitrogenic agent).

1. Defects Found in Drafted Men, War Dept. (1920).
2. Bratton, McClendon, Foster and White: *Ind. & Eng. Chem., Anal. Ed.* 10: 600. 1938.
3. McClendon: Iodine and the Incidence of Goiter, p. 21, University of Minnesota Press, 1939.

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PROBLEMS OF AGING

The National Institute of Health of the United States Public Health Service is organizing a new unit for research into some of the many problems of aging. With the conspicuous shift to greater age in the population, senescent individuals are becoming increasingly significant in the national economy and defense. Preventive medicine must attack the practical problems of the rising proportion of deaths attributable to diseases of middle and later life and energetically attempt to augment the health and vigor of those past the meridian. Aging is a continuous biologic phenomenon which starts upon creation of a new individual and continues at variable rates until death. The problems of aging (gerontology) are not limited to the diseases of the aged (geriatrics), for the latter are the consequences of senescence. In man probably the most significant period of life for gerontologic study is late maturity, approximately the two decades between 40 and 60.

The problems of aging are logically divisible into three major fields of investigation: (1) the biology of senescence as a process, (2) the human clinical problems of aging and of diseases characteristically associated with advancing years which include the mental changes of senescence and senectitude as well as the physical changes, and (3) the socio-economic problems of a shifting age distribution in the population. The National Institute of Health is concerned with the first two of these divisions of the science.

In order to advise this new unit, there has been formed a National Advisory Committee on Gerontology, representative of the scientific thought of the nation. The membership of this Advisory Committee includes:

Dr. L. R. Thompson, Director, National Institute of Health, U. S. Public Health Service

Dr. Anton J. Carlson, Physiologist, University of Chicago, National Research Council

Dr. Charles L. Christiernin, Association of Life Insurance Medical Directors of America; Medical Director, Metropolitan Life Insurance Co.

Dr. Robert A. Coker, Zoologist, University of North Carolina

Dr. William Crocker, Botanist, Boyce Thompson Institute of Plant Research

Mr. Lawrence K. Frank, Sociologist, Josiah Macy, Jr. Foundation

Dr. A. Baird Hastings, Biochemist, Harvard University
Dr. Ludvig Hektoen, Pathologist; Consultant, National Cancer Institute, U. S. Public Health Service
Dr. Winfred Overholser, Psychiatrist; Superintendent, St. Elizabeths Hospital
Dr. Clarence Selby, Industrial Physician, General Motors Corporation
Dr. William D. Stroud, Clinician, Philadelphia, Pa.

The first service to scientific research which the Unit on Gerontology is undertaking is to conduct a survey of the present trends of active and contemplated investigations into the problems of aging in American scientific institutions. This survey is intended to ascertain just what problems are being studied and what methods of approach are being applied. There is no desire to learn, in advance of publication, the data being developed in these specific undertakings.

In addition to these studies, many investigations which do not pertain directly to aging should yield data useful to workers in gerontology. The Unit on Gerontology is especially interested in knowing of these indirectly related studies, the full implications of which are far too often obscured in their published titles.

Inquiries about studies related to aging are being sent to scientists in the basic biologic sciences as well as to clinical investigators, for much fundamental work upon the processes, mechanisms and consequences of senescence is probably going on in the sciences of botany, zoology, physiology, pharmacology and psychology. From the clinical viewpoint, our greatest concern is with those studies dealing with health evaluation, mensuration of functional capacity (including criteria of 'physiologic age') and with those diseases whose incidence increases sharply in later life (the so-called degenerative disorders).

Critical analysis of the information elicited by such a survey may be expected to serve several valuable purposes. It should assist in bringing together in closer cooperation investigators interested in related problems, especially when widely divergent methods of approach are being utilized. The survey will likewise emphasize the urgent need for greatly augmented support for significant studies of these vitally important problems of senescence.

The broad and general pattern of the problems being investigated will undoubtedly reveal a number of neglected 'blank spots' which may justify special emphasis in the future. Analysis of the data of the survey will also be an invaluable aid in formulating future research programs, both at the National Institute of Health and elsewhere.

From preliminary inquiries it is observed that there is a great but largely latent and scattered interest in the problems of aging. It is the hope of the unit of gerontology of the National Institute of Health that the present survey may serve to effectively aid the promotion of closer cooperation of the scientists interested in these fields.

Information concerning subjects under investigation and the methods of approach is earnestly solicited.

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NECROSPERMIA

It has recently been shown that spermatozoa can withstand abnormally low temperatures (0° C., freezing; minus 196° C., liquid nitrogen; and minus 269° C., liquid helium) and can survive for as long as 36 to 48 hours at ordinary room temperatures (20 to 23° C.). However, death of spermatozoa after ejaculation may be brought about quite easily and rapidly owing to faulty methods of collection. A microscopic examination of the killed sperms leads to the diagnosis of total necrospermia, and the patient may be told that he is sterile since all his spermatozoa are found dead (immotile).

Twelve selected male patients whose seminal fluid had been previously tested by different examiners illustrate the frequency of the erroneous diagnosis of necrospermia. In each instance, the patient had been informed that many sperms were found but that all were dead. Since these men had been found deficient and the responsibility for the conjugal sterility had been placed upon them, their spouses were not thoroughly examined. Following the semen findings, 5 of the patients had submitted to some form of injection therapy in an attempt to "improve" their sperms. The other 7 had been advised to either adopt a child or to encourage their wives to resort to artificial donor inseminations.

These 12 males were referred by physicians who questioned the earlier diagnoses of necrospermia and who desired a more thorough semen analysis to be able to better evaluate the male deficiency. In every instance, the semen was collected by masturbation, with ejaculation into a sterile, dry, wide-mouth glass specimen jar. The semen specimens were now carefully analyzed for volume, pH, turbidity, viscosity, mucolysis, counts, morphology, motility, viability, resistance to temperatures and acids, and survival at ordinary room temperatures. The detailed findings of the specimens were interesting but they are not within the scope of this communication. It should suffice to mention but a few of the salient points from the semen analyses.

In every case the semen presented live spermatozoa. Two of the specimens were far better than normal in count, morphology and motility. Six of the seminal fluids could be considered to be of average fertility. The remaining 4 specimens were rather poor but not one of these 4 poor specimens contained less than 16,000,000 living spermatozoa in each cubic centimeter of semen.

Upon checking back at the earlier diagnosis of total necrospermia, it was brought to light that in each instance the patient transported his semen to the examiner in a rubber condom. The time that elapsed between the ejaculation and the arrival of the condom specimens varied from ½ to 2½ hours. The death of the spermatozoa could therefore be definitely traced to the male sheaths. The chemicals used in the manufacturing process of rubber refinement and the chemical dusting powders with which many of the condoms are treated have been shown to be drastic spermicides.

The undesirability of the condom method of collection of semen should be more generally recognized.

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Abstracts of
CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, ERICH VON HAAM.

GONADS

HESSELTINE, H. C., F. L. ADAIR AND M. W. BOYNTON.

Limitation of human reproduction: therapeutic abortion. *Am. J. Obst. & Gynec.* 39: 549. 1940.

An analysis of 134 therapeutic abortions performed at the Chicago Lying-In Hospital led to the following conclusion. (1) Therapeutic abortion is a necessary, but relatively infrequent, obstetric procedure. (2) It should be done only to save or to prolong significantly the life of the mother, or to prevent the transmission of serious hereditary defects. (3) It should be attempted only after adequate consultation, only in reputable hospitals, only by competent operators, and only after both the husband and wife (or legal guardian) consent. (4) It is rarely, if ever, an emergency procedure, and should not be undertaken until the patient is in the best possible condition for it. (5) It is not without some risk of operative complications, and even fatality. (6) Sterilization is indicated whenever the same problem would arise in a subsequent pregnancy. —Authors' abstract, from *Clinical Abstracts.*

HUBER, C. P., AND M. E. DAVIS.

The clinical use of gonadotropic hormone from pregnant mare serum. *Surg., Gynec. & Obst.* 70: 996. 1940.

Administration of gonadotropic hormone from PMS was followed by pregnancy in previously sterile patients in whom anovulatory menstrual cycles had been demonstrated. The hormone proved clinically effective in some cases of acyclic uterine bleeding associated with evidence of continued endometrial proliferation. Amenorrhea resulting from inadequate ovarian activity responded to the PMS hormone by the occurrence of uterine bleeding. No untoward effects have been demonstrated either locally or systemically following several hundred intramuscular and intravenous injections. Further carefully controlled clinical observations are necessary for definite establishment of the therapeutic value and the indications for use. —From authors' abstract.

HUFFMAN, J. W.

An evaluation of androgenic therapy in gynecologic practice. *Am. J. Obst. & Gynec.* 40: 675. 1940.

Following an epitome of experimental work with androgens in respect to therapy, the author discusses 22 cases with a clinical diagnosis of functional bleeding which received androgen therapy. Functional flow and menstruation were stopped at a dosage of 25 mg. testosterone propionate every other day, with usually 10 to 15 injections, or a total of 250 to 450 mg. Smaller doses, 10 mg. twice weekly, usually decreased the amount of menstrual bleeding and shortened its duration without complete inhibition. Patients who received 400 mg. or more tended to develop definite hypertrophy of the clitoris which disappeared upon androgen withdrawal. Vaginal smears revealed almost complete absence of estrogenic activity. In view of his results and of an extensive literature, the author believes androgen therapy has a place in treatment of functional uterine bleeding, mastalgias and puerperal breast engorgement and for inhibition of lactation, as well as for selected cases of menopausal disturbances. An extensive review is given of pertinent literature.—H.O.H.

LACKNER, J. E., AND A. S. TULSKY.

The effect of human pregnancy serum on uterine motility. *Endocrinology* 27: 41. 1940.

An attempt was made to elicit contractions in the human nonpregnant uterus as detected by the intrauterine bag, by the use of intravenously administered human parturient serum. In a series of 16 experiments on 10 essentially normal ♀ ♀, in no case was there a demonstrable response of the uterus to this material, whether obtained from a toxemic or nontoxemic ♀ in labor. Blood serum derived from a ♀ in labor either contains no oxytocic substance, or such small amounts as to have no effect on the human uterus in vivo, in the dosage or manner employed.—Authors' summary.

LIN, HAZEL AI-CH'ÜN.

The quantitative determination of urinary estrogens in cases of uterine hemorrhage. *Chinese M. J.* 57: 216. 1940.

Daily output, as measured by bioassay, was low in 6 cases of metropathia hemorrhagica.—C. D. Stevens.

MCCULLAGH, D. R., I. SCHNEIDER, AND F. EMERY.

Spectrophotometric studies of the m-dinitrobenzene reaction with sex steroids. *Endocrinology* 27: 71. 1940.

Spectrophotometric curves were run of the color produced by the reaction of m-dinitrobenzene and the following steroids: androsterone, dehydroandrosterone, estrone, androsterone, benzoate, testosterone, methyl testosterone, cholestenone, pregneninolone, pregnenolone, alpha-estradiol and androstendiol. A similar study was made on extracts of human ♂ blood, bovine testis tissue and normal human ♂ urine. These curves could not be

related to those observed using pure steroids. The curves for the 17-ketosteroids were qualitatively and quantitatively almost identical. Similarly, the curves for the 3-ketosteroids were all very similar but differed markedly from the 17-ketosteroids. Pregnenolone, a 20-ketosteroid, was again different in that it showed a similar reaction to the 17-ketosteroids, but differed markedly in total transmission. The non-ketonic diols did not react with m-dinitrobenzene.—Authors' summary.

McCullagh, E. P.

Peroral use of methyl testosterone in testicular deficiency. *Cleveland Clin. Quart.* 7: 226. 1940.

Methyl testosterone was given in tablets of 25 mg. in dosages of 25 to 75 mg. per day, and as much as 150 mg., for various types of testicular failure and for impotence. Results appeared within a few weeks. Effectiveness as compared with testosterone propionate approximated the ratio of 3 to 4 to 1. Its metabolism differed in that clinically effective doses of testosterone propionate were followed by an increase in urinary androgen. With methyl testosterone this sequence did not occur to the same extent.—H.O.H.

McCullagh, E. P., and W. K. Cuyler.

Positive Friedman tests in nonpregnant states. *Am. J. Clin. Path.* 10: 593. 1940.

Of 2134 cases tested, 241 were positive in which neither pregnancy nor evidence of chorionic tissue resulted. Of 1,974 tests in women 172 were positive and of 360 tests in men 69 were positive. The tests were made on persons suspected of some endocrine abnormality and not of pregnancy. The positive cases were broken down into several groups—1) conditions peculiar to ♀ disorders, 2) conditions associated with or due to testis deficiency or tumor, 3) endocrine disorders not sex specific, 4) disorders of the nervous system, 5) pituitary and 6) not clearly endocrine in nature. It is emphasized that the test is frequently positive at puberty, may be positive in psychoses, hysteria, epilepsy, and arterial hypertension in absence of gonadal failure and may be useful in differential diagnosis of pituitary cachexia and anorexia nervosa. Primary pituitary disorder, acromegaly or tumor, and organic lesions of the hypothalamus may cause positive reactions. Positive reactions have been found in dwarfism and obesity, suggesting that gonadal failure, when present, might not be due to gonadotropic hormone deficiency. The test may be positive in hyperthyroidism, in diabetes mellitus, and adrenal cortical hyperfunction. Gonadal damage in either sex may produce a positive test, and hence it is frequently positive at the menopause and in ♀ ♀ with functional ovarian deficiency, ovarian tumors and ovarian inflammation. It may be positive also in ♂ ♂ with testicular deficiency, cryptorchidism and prostatic hyptertrophy—From *J.A.M.A.* Abstracts.

Moore White M.

Some investigations on the treatment of sterility. *Proc. Roy. Soc. Med.* 33: 517. 1940.

A comparison was made between uterosalpingography and tubal insufflation, and the relative diagnostic and therapeutic values of each discussed, with the claim that lipiodol injection has a higher therapeutic value and tubal insufflation affords a better means of diagnosis. Lipiodol injections were given 161 patients Twenty-eight and three-tenths % of the total number became pregnant, and 47.3% of those in whom no obvious cause for infertility in either husband or wife was found. The corresponding figures in 48 insufflations were 10.4% and 25%. The effect of follicular hormone in non-patent fallopian tubes was demonstrated in 9 cases, and on tubes showing partial patency and absence of peristalsis in 4 cases. In 9 instances patency resulted, tubal contractions were obtained in 8, poor in 2 instances. There was no improvement in 4 cases, 3 patients became pregnant, although 2 miscarried. In 7 patients who had remained sterile after exclusion of other known possible factors, endometrial biopsies showed evidence of corpus luteum deficiency. This deficiency was supplemented in 6 cases, 2 patients became pregnant, and a 3rd probably became pregnant, although her subsequent history could not be obtained. One miscarried.—From author's summary.

Pattee, C. J., E. H. Venning and J. S. L. Browne.

The effect of estrogens on the pregnandiol output during the menstrual cycle. *Endocrinology* 27: 720. 1940.

Pregnandiol excretion was studied in 3 cases which received estradiol benzoate (20,000 to 80,000 I.U.) during the menstrual cycle. Output was decreased in all cycles. In 1 case corpus luteum formation appeared to be prevented by 10,000 I.U. given daily on the 11th, 12th, and 13th days. In another case the same dose on the 9th, 11th and 13th days failed to prevent corpus luteum formation. Injection of estradiol benzoate commenced after the luteal phase had started also decreased the output of pregnandiol in that cycle.—From authors' summary.

Rea, C. E.

Treatment of the undescended testes by hormonal therapy. *Surgery* 7: 828. 1940.

In 2 series of retained testes degrees of descent were obtained in not more than 20% of cases. One reason for the successful results in some cases is undoubtedly inclusion of cases of pseudo-cryptorchidism. Final estimation of the value of gonadotropic substance in treatment is impossible at present, since the incidence of spontaneous descent is unknown. Hormonal therapy makes it possible to differentiate between those testes which require surgical intervention because of mechanical obstruction and those which do not. Treatment should be deferred until 9 to 11 years, since the testes do not grow grossly or microscopically until then and since it is possible that spontaneous descent may occur. In the writer's experience, spontaneous descent or descent following use of gonadotropic substance in cases of true undescended testes is a rare occurrence. Every case of true undescended testis upon which an orchipexy has been performed has shown evidence of mechanical arrest to descent.—From author's summary.

RENNIE, T. A. C., S. A. VEST AND J. E. HOWARD.

The use of testosterone propionate in impotence. *South. M. J.* 32: 1004. 1939.

Eight cases of psychic impotence and 1 ♂ homosexual patient were treated with testosterone propionate. In none was any improvement noted. The authors conclude that if the factor of suggestion is excluded it is very unlikely that doses of specific ♀ hormone adequate for excellent responses in hypogonad patients are of any benefit therapeutically in the type of patient reported.—J. A. McAlpine.

ROTHERMICH, N. O., AND L. M. FOLTZ.

A comparative study of the effects of male and female sex hormones on pituitary gonadotropic function in women. *Endocrinology* 27: 37. 1940.

In 5 of 7 menopausal women treated with large doses of estrogenic hormone, the urinary excretion of gonadotropic hormones could be reduced to within normal limits. 3 of 4 cases responded in a similar manner to the administration of ♂ sex hormone. In the 2 cases apparently refractory to the estrogen, a definite decrease of urinary gonadotropin could be produced by administration of androgen. Administration of both hormones simultaneously and in varying doses resulted in a temporary nullification of the effects of one by the other, depending upon the doses given.—Authors' summary.

RYAN, E. J.

Ovarian hormone therapy in functional menometrorrhagia: preliminary report. *Cleveland Clin. Quart.* 7: 197. 1940.

Cyclic treatment was employed, given on basis of 28-day cycles, with admin. of 2,000 R.U. estradiol benzoate or 10,000 I.U. estrone 2 or 3 times per week for 1st 3 weeks and, during the 4th week, 2 to 5 mg. progesterone on the 5th and 3rd days before onset of the calculated menstrual period. Therapy then was withheld for 3 to 5 days and begun again. After 4 to 6 months therapy was withheld to determine normality of menstrual rhythm. A case is presented to illustrate method and results.—H.O.H.

SALMON, U. J., S. H. GEIST, AND R. I. WALTER.

Evaluation of stilbestrol as therapeutic estrogen. *Am. J. Obst. & Gynec.* 40: 243. 1940.

While capable of relieving menopausal symptoms and of showing an estrogen-like effect on vaginal mucosa and on endometrium, stilbestrol did not offer the complete relief from nervous instability afforded by the natural estrogens. Toxic symptoms in 65% of 45 patients militates against its usefulness as a therapeutic agent.—H.O.H.

SEEGAR, G. E., AND E. DELFS.

Pregnandiol excretion following bilateral oöphorectomy in early pregnancy. *J.A.M.A.* 115: 1267. 1940.

In the case presented all ovarian tissue was removed on the 63rd day, with no subsequent clinical abnormalities during pregnancy and parturition. The excretion of pregnandiol remained far below that found in normal pregnancy, and only twice did it exceed values found in nonpregnant cyclic women. That pregnandiol was excreted at all supports the theory of an extra-ovarian source of the corpus luteum hormone.—H.O.H.

SHINOWARA, G. Y., AND H. L. REINHART.

The estimation of sodium pregnandiol in urine. *Am. J. Clin. Path.* 10: 77. 1940.

The method described is essentially that of Venning, e.g., extraction with butyl alcohol, precipitation with acetone, and gravimetric determination of the precipitate. Certain minor modifications were introduced, as, for example, in nongravid patients 2 acetone precipitations were necessary because of high percentage of impurities, and mention is made of the frequent necessity for centrifugation to break the heavy butyl alcohol-urine emulsion in the 1st series of extractions. To check accuracy each investigator is urged to apply the procedure outlined on urine containing a known amount of sodium pregnandiol glucuronidate.—H.O.H.

SPENCE, A. W.

Testosterone propionate in functional impotence. *Brit. M. J.* 2: 411. 1940.

Six patients with functional impotence unassociated with any evidence of testicular dysfunction failed to respond to testosterone propionate, given intramuscularly in doses of from 50 to 100 mg. thrice weekly for 2 to 6 weeks. A 7th patient with hypogonadism also failed to respond after treatment for 2 months probably because of a superadded psychological disturbance. As these doses are sufficient to produce prolonged erections in eunuchs, it is concluded that testosterone propionate has no effect on impotence due to psychological disturbances.—Author's summary.

SPIEGELMAN, A. R.

Influence of estrogen on the insulin requirement of the diabetic. *Am. J. M. Sc.* Vol. 200: 228. 1940.

The administration of 10,000 I.U. of estrogenic hormone twice a week to a series of 9 diabetic women was associated with a diminution in their insulin requirement. The average daily insulin requirement did not return to the "pre-estrogen" level even after estrogen had been discontinued for a period of 3 months. The type of insulin used in the control diabetes had no influence on the results obtained. In the premenopausal group the diminution in the insulin requirement associated with the administration of estrogen was greater and more sustained than in the postmenopausal group.— Author's abstract.

v. HAAM, E., AND N. O. ROTHERMICH.

Excretion of gonadotropic and estrogenic hormones in urine during normal menstrual cycle. *Proc. Soc. Exper. Biol. & Med.* 44: 369. 1940.

Daily bioassays of the urines of 3 healthy women during 1 menstrual cycle showed several peaks of prolan excretion in a single cycle. The excretion of estrin either paralleled or in some instances proceded the prolan excretion. One or 2 peaks were distinguishable.—E. von Haam.

WALTER, R. I., S. H. GEIST AND U. J. SALMON.

Absorption rates and biologic effects of pellets of α-estradiol and α-estradiol benzoate in women. *Proc. Soc. Exper. Biol. & Med.* 44: 314. 1940.

In a series of 114 cases the average % absorption rate per 30 days for α-estradiol pellets was 4.85% (473 R.U. per day), as compared to 1.72% (113 R.U. per day) for pellets of α-estradiol benzoate. The duration of biologic and therapeutic effects was definitely longer in the α-estradiol series. The fibrous capsule which formed about the pellets progressively decreased the rate of absorption. Moreover, because absorption of the hormone in effective amounts ceased when only a relatively small proportion of the pellet had been absorbed, it was concluded that the implantation of pellets weighing 15 to 25 mg. of α-estradiol and α-estradiol benzoate is evidently not a satisfactory method of administering estrogens.—U. J. Salmon.

WEED, J. C., B. B. WEINSTEIN, F. R. LOCK, J. W. DOUGLAS AND C. G. COLLINS.

The oral administration of stilbestrol. *Am. J. Obst. & Gynec.* 39: 1047. 1940.

The results of oral administration in menopausal syndromes, physiologic and artificial and hypoestrinism lead to the following recommendations. (1) That therapy be individualized. (2) That the initial dosage be at least 1 mg. 3 times a day, and be varied as indicated. (3) When symptoms are improved that the amount be reduced to a satisfactory maintenance dose. (4) That the tablets be powdered and administered in milk.—From author's abstract, in *Clinical Abstracts*.

WEINSTEIN, B. B., J. C. WEED, F. R. LOCK AND C. G. COLLINS.

Oral administration of diethyl stilbestrol dipropionate. *Endocrinology* 27: 739. 1940.

In 51 cases of physiological menopausal syndrome 25 were relieved, 16 were improved, 3 only slightly, and 7 failed to respond to a dosage of 1 mg. T.I.D. for 1 week with subsequent individualization of therapy. Six cases of hyperestrinism showed relief, and relief was obtained in 8 cases of senile vaginitis. In the latter cases, however, symptoms frequently recurred after withdrawal of treatment. The only toxic manifestations shown were nausea and, to a less extent, vomiting, which appeared in 15% of the patients. The authors emphasize individualization of therapy, once a degree of response is ascertained.—H.O.H.

WILSON, L.

Action of testosterone propionate in a case of endometriosis. *Endocrinology* 27: 29. 1940.

A total of 4,800 mg. of testosterone propionate was administered over a period of 13 mo. to a ♀ with endometriosis of the recto-vaginal septum with suppression of menstruation for 1 year, marked but incomplete reduction of the size of the tumor with complete freedom from pelvic pain, atrophy of the uterine mucosa, persistent hoarseness, progressive hirsutism, and enlargement of the clitoris. When treatment was discontinued ovarian function was promptly and fully restored with subsequent revival of the growth of the tumor and return of the pelvic pain. The masculinizing effects slowly regressed so that 6 mo. after discontinuation of the treatment the voice was practically normal, the clitoris was only slightly enlarged and the hirsutism was of minor degree. Hormonal sterilization (by means of testosterone propionate) affects the growth of ectopic endometrium similar to surgical and radiation sterilization. It differs in that the effects are temporary and persist only for the duration of the therapy; and masculinizing phenomena are almost certain to result because of the large doses of ♂ sex hormone that are required. These 2 differences seriously impair its value as a practical method of treating cases of endometriosis.—Author's summary.

WILSON, L., AND R. KURZROK.

Uterine contractility in functional dysmenorrhea. *Endocrinology* 27: 23. 1940.

Functional dysmenorrhea is a psychogenic disorder in which a reduced pain threshold or a disturbed pelvic autonomic nervous system permits normal uterine contractions during the phase of maximum amplitude to reach consciousness. Dysmenorrhea occurs only in the presence of a functional corpus luteum and the normal myometrial cycle. The absence of dysmenorrhea in anovulatory cycles is attributed to the absence of the large luteal-phase contractions. The administration of estrogens and other gonadal hormones in large doses early in the menstrual cycle frequently abolishes or diminishes the pain of the subsequent period. This effect can be attributed to reduction of uterine motility (via the hypophysis and ovary) only when the ensuing period occurs prematurely. If the cycle is of normal duration or is prolonged, the contractions at the time of the flow are of the usual large amplitude. Yet in these cases too the pain is frequently absent.—Authors' summary.

WINKELSTEIN, A.

A possible relationship between the ductless glands secreting the sex hormones and peptic ulcer. *J. Mt. Sinai Hosp.* 7: 29. 1940.

Clinical and experimental observations are cited which suggest that an unchecked or hyperactive pituitary may be associated with increased gastric secretion and ulceration. On this basis, estrogen therapy is suggested for inhibition purposes. Such therapy was instituted with good results in a small group of patients in whom ulceration appeared at the menopause. The possibility of extending these studies to the use of estrogen, progesterone and androgen in the study and therapy of peptic ulcer generally, is tentatively suggested.—Author's abstract.

WOLFE, J. T.

Hypodermic use of adrenalin chloride for relief of menstrual cramps. *Virginia M. Monthly* 67: 548. 1940.

Seven patients with dysmenorrhea were given hypodermic injections of epinephrin on the theory that contraction rings and menstrual cramps are produced by spasm of the cervical and uterine muscle fibers and that they can be relieved through the autonomic nervous sys-

tem by stimulation of the sympathetics. Five of the patients had a less severe type of disorder, with prompt response and expression of relief within 5 minutes of the injection.—From *J.A.M.A.* abstracts.

ZELSON, C., AND E. STEINITZ.

Treatment of cryptorchidism with chorionic gonadotropic hormone and male sex hormone. *J. Pediat.* 17: 315. 1940.

Seventeen boys with cryptorchidism, two bilateral, received a course of combined treatment with injection of chorionic gonadotropic hormone (pregnyl) and testosterone propionate (neo-hombreol). Each injection contained 500 R.U. of gonadotropic hormone and 5 or 10 mg. testosterone propionate. Nine (53%) responded with complete descent of the testes, some of whom had not responded previously to either hormone alone or successively. Treatment should be instituted before the 10th year.—From authors' summary.

ZONDEK, B.

The effect of prolonged administration of estrogen on the uterus and the anterior pituitary of human beings. *J.A.M.A.* 114: 1850. 1940.

Some cases treated with large doses of estrogen showed postponement of menses, with 70,000 U or more from 7 to 70 days. Large doses caused blocking of gonadotropic secretion of the pituitary, thereby impairing development of the corpus luteum. The larger doses caused glandular cystic hyperplasia of the uterine mucosa. There was marked increase in pituitary eosinophilic cells, a genuine adenoma being found in 1 case.—E. A. Baumgartner.

ZONDEK, B., S. ROZIN AND M. VESELL.

Uterine bleeding induced by progesterone. *Am. J. Obst. & Gynec.* 40: 391. 1940.

Bleeding of 3 to 5 days duration was induced during the intermenstrual stage by a total dosage of 50 mg. progesterone parenterally in the postmenstrual stage. If administered at the time of follicular rupture no intracyclic bleeding occurred. Pregneninonal per os was equally effective. Large doses of estrogens, however, prevented occurrence of progesterone-induced intracyclic bleeding. Bleeding occurred in secondary amenorrhea some 60 to 72 hours following administration of 50 mg. over 5 days. In 50% of cases one course of progesterone treatment improved secondary amenorrhea for several months. Progesterone was able to induce bleeding from a thin mucous membrane as well as from a fully proliferated or a progestational one. In primary amenorrhea progesterone alone was ineffective, but required supplement with small amounts of estrogen.—From authors' summary.

HYPOPHYSIS

BAILEY, O. T., AND E. C. CUTLER.

Malignant adenomas of the chromophobe cells of the pituitary body. *Arch. Path.* 29: 368. 1940.

Three cases, 2 ♂♂, 1 ♀, of tumors arising from the chromophobe cells of the pituitary are described. The early stages of illness were dominated by ocular symptoms, uncinate seizures and nasal obstruction. The common characteristics noted were a relatively short history, a rapid extension into both bone and neighboring brain substance, and into the nasopharynx. Histologically, the tumor cells were arranged in broad sheets separated by a stroma which was altered in character from that of the pars anterior, and was derived from the structures at the edge of the tumor far from the sella. One of the patients showed a satisfactory response to biopsy followed by x-ray therapy. Two patients treated surgically died.—L. B. Shpiner.

CANAVAN, M. M.

Simmonds' disease (pituitary cachexia) in an aged man with dementia praecox. *Arch. Path.* 29: 310. 1940.

A ♂ patient aged 72, having dementia praecox died 3 months after fracture of a femur. Marked emaciation occurred after the accident with a total weight loss of 90 lb. At autopsy the pituitary presented a small and edematous appearance. Microscopically, varying degrees of degeneration of the cells in the anterior lobe was noted. This was especially marked in the acidophil population.—L. B. Shpiner.

DOANE, J. C., N. BLUMBERG AND G. TEPLICK.

Simmonds' cachexia. *Endocrinology* 27: 766. 1940.

Two cases are reported, one with autopsy findings, the other successfully treated with APL substance. The autopsied case revealed an unusual anterior pituitary pathology in complete absence of eosinophil cells. Simmonds' disease may be due not only to an organic destruction of the anterior pituitary, but also to a functional suppression, and hormone assays should always be made to confirm a doubtful diagnosis, especially where anorexia nervosa seems a possible alternative. In Simmonds' disease gonadotropins are apparently absent from urine. Hypopituitarism may give rise to a very mild form of this disease, often unrecognized as such.—Authors' summary.

DORFMAN, R. I., H. M. WILSON AND J. P. PETERS.

Differential diagnosis of basophilism and allied conditions. *Endocrinology* 27: 1. 1940.

Arrhenoblastomas are seldom if ever attended by the circulatory or metabolic disorders which usually characterize basophilic and corticoadrenal syndromes. True virilism occurs only with adrenal cortical tumors or hyperplasia and with arrhenoblastoma. In the former conditions the urine contains excessive amounts of materials having androgenic activity. If the condition appears before growth is completed corticoadrenalism gives rise to precocious development and precocious union of the epiphyses; while in basophilism development and epiphyseal union appear to be retarded. In no case of this series in which it was measured did urinary estrogenic activity exceed normal limits.—Authors' summary.

GREENE, J. A., AND L. E. JANUARY.

Diabetes insipidus treated by the subcutaneous administration of a suspension of pitressin tannate in oil. *J.A.M.A.* 115: 1183. 1940.

Pitressin tannate in oil administered in 1 cc. injections

to 5 patients with d.i., and to 3 experimentally d.i. cats. The duration of the effect in the cats varied 3 to 7 days and in the patients 30 to 82 hours. The clinical effect was equal to that of other preparations of posterior pituitary gland, and no disagreeable side effects were noted.—H. O. H.

LOEWENBERG, S. A., AND N. G. SLOANE.

Diabetes insipidus of over twenty years' standing improved following a subarachnoid hemorrhage. *Endocrinology* 27: 191. 1940.

A case of d.i. with moderate hypertension, of approximately 20 years duration, that has improved in both the d.i. symptoms, and in the hypertension, following a spontaneous subarachnoid hemorrhage. The hemorrahge was probably due to the rupture of a small aneurysm of the circle of Willis; when the aneurysm was intact, it exerted pressure at the base of the brain in the pituitary hypothalamic region, and the removal of pressure in that region caused definite amelioration of symptoms. A total cure is hardly to be expected in a case of such chronicity as definite changes interfering with normal function may possibly have taken place in that portion of the brain which is said to be responsible for diabetes insipidus.—Authors' summary.

MCGAVACK, T. H., J. W. BENJAMIN AND S. LIEBOWITZ.

Diabetes insipidus. *Arch. Neurol. & Psychiat.* 44: 867. 1940.

A case of d.i., probably secondary to postinfectious encephalitis, is reported. Typical responses were obtained to ingestion and deprivation of water and salt, and to administration of solution of posterior pituitary, U.S.P. Bilateral degeneration of the supraoptic nuclei and the posterior lobe of the pituitary gland were observed in the hypothalamus at necropsy.—From author's summary.

MAGENDANTZ, H., AND S. PROGER

Anorexia nervosa or hypopituitarism? *J.A.M.A.* 114: 1973. 1940.

Three cases are reported, 2 girls aged 14, and 1 woman aged 28 with markedly similar loss of weight, lack of appetite, constipation, cessation of menses. These cases showed dry skin, normal or subnormal temperatures, often a pulse as low as 35, low fasting blood sugars and a flat slowly rising sugar tolerance curve, and a low urinary output in which nothing otherwise abnormal was found. The patients were depressed, sullen, morose, and were so similar in findings to the so-called fatal Simmonds' disease that they may be regarded mild forms, although there were striking psychic abnormalities. The etiology is obscure, and no satisfactory treatment is known. Some recover spontaneously, after extensive medication has failed to produce results.—E. A. Baumgartner.

NEUFELD, A. H., S. M. SCOGGAN AND G. S. STEWART.

The effect of pituitary preparations on the total body glycogen, water, nitrogen and fat of mice. *Endocrinology* 27: 132. 1940.

The administration of certain anterior pituitary preparations to normal fasted mice (dba) resulted in a rise of total body glycogen, associated with a low fatty acid content. The distribution of fatty acids between liver and carcass suggested an increased fatty acid oxidation. The water retention observed may be accounted for by the antidiuretic potencies of the extracts. Total body N and its distribution between liver and carcass do not appear to be affected to any appreciable extent. The unusually high glycogen values observed in animals treated with the saline extract of fresh anterior lobes may be associated with the diabetogenic substance.—Authors' summary.

RAWSON, R. W., AND W. T. SALTER.

Microhistometric assay of thyrotropic hormone in day-old chicks. *Endocrinology* 27: 155. 1940.

The method can be performed on readily available biological material; it combines technics which have already been tested thoroughly and it gives such high sensitivity that a numerical evaluation of thyrotropic activity can be had for concs. of thyrotropic hormone as low as those found in normal human urine. Furthermore, it can easily be calibrated against known standard material by each investigator so that results are readily interpretable elsewhere.—Authors' summary.

STOESSER, A. V., AND M. M. COOK.

Electrolyte and water exchange in bronchial asthma, with emphasis on the influence of pitressin. *J. Allergy* 11: 557. 1940.

Six asthmatic children who tolerated the hormone were placed on a low NaCl diet and with pitressin administration retention of water up to 2 kg. occurred in some cases. Improvement of asthma began during the antidiuretic phase and continued through the diuretic and subsequent periods, proving storage of large amounts of water and its sudden loss had little influence on asthmatic symptoms. It is apparent that bronchial asthma can be ameliorated even in the presence of excessive hydration, if there is an associated depletion of NaCl.—H.O.H.

WESTMAN, A.

Clinical and experimental studies on transplantation of the hypophysis. *Acta Obst. et Gynec. Scandinav.* 20: 118. 1940.

The pituitary bodies from calves were transplanted to a series of cases with primary and secondary amenorrhea which were not permanently improved with ovarian or gonadotropin treatment. Results obtained in treatment with transplants in Simmonds' disease indicated that grafts may exercise a stimulating effect on the ovaries. As opposed to those results however experiments with transplantation of pituitary glands in rats showed the transplanted substance to have no gonadotropic activity. In 10 cases calf glands were transplanted. In 2 cases there were no effects; in 8 bleeding appeared. These two cases differed from the rest in that, besides amenorrhea, other endocrine disturbances indicating a pituitary deficiency were present. Probably the hormonal substances present in the transplants stimulated the pituitary glands of the patients into stronger activity. Microscopic examination of grafts was not made, but the author feels it improbable they have persisted.—From author's summary.